STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 196651

TO: Ralph J Gitomer
Location: REM/3D65/3C18
Art Unit: 1655
Tuesday, July 11, 2006

Case Serial Number: 10/029372

From: Deirdre Arnold
Location: Biotech-Chem Library
REM 1A55
Phone: 571-272-2532

Deirdre.Arnold@uspto.gov

Search Notes

Beware of false hits on the names in the inventor search.

Please feel free to contact me if you have any questions or would like to amend the search.

Thank you for using STIC services.

Regards,
Deirdre Arnold

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=> d que stat l78
L1             1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  US2001-29372/APPS
L3               TRANSFER  PLU=ON  L1 1- RN :      24 TERMS
L4            24 SEA FILE=REGISTRY ABB=ON  PLU=ON  L3
L7               QUE  ABB=ON  PLU=ON  AY<2001 OR PY<2001 OR PRY<2001 OR MY
                 <2001 OR REVIEW/DT
L10              QUE  ABB=ON  PLU=ON  ?SPHINGO? OR ?CERAMID? OR KETOSPHING
                 ? OR GALACTOSYLCERAMID? OR DIHYDROCERAMID?
L11              QUE  ABB=ON  PLU=ON  CEREBROSID? OR ?PALMITOYLTRANSFER? O
                 R (?PALMITOYL?(1A)TRANSFERAS?) OR (NADPH(3A)REDUCTAS?)
L12              QUE  ABB=ON  PLU=ON  HEART? OR ?CORONAR? OR ?CARDIO? OR ?
                 CARDIA? OR MYOCARD?
L13              QUE  ABB=ON  PLU=ON  ISCHEM? OR POSTISCHEM? OR REPERFUS?
                 OR NEOVASCUL? OR (NEO(W)VASCUL?) OR ANGIOGEN? OR (ANGIO(W
                 )GENE?) OR STENT? OR ?STENOSIS? OR RESTENOSIS? OR STROKE?
L14              QUE  ABB=ON  PLU=ON  ?CEREBR? OR BRAIN
L15              QUE  ABB=ON  PLU=ON  VASCU? OR VEIN? OR ARTER?
L19              QUE  ABB=ON  PLU=ON  SURGERY+PFT,OLD,NT/CT
L20              QUE  ABB=ON  PLU=ON  ISCHEMIA+PFT,OLD,NT/CT
L21              QUE  ABB=ON  PLU=ON  STROKE+PFT,OLD,NT/CT
L22              QUE  ABB=ON  PLU=ON  "HEART, DISEASE"+PFT,OLD,NT/CT
L23              QUE  ABB=ON  PLU=ON  REPERFUSION+PFT,OLD,NT/CT
L24              QUE  ABB=ON  PLU=ON  "BRAIN, DISEASE"+PFT,OLD,NT/CT
L25              QUE  ABB=ON  PLU=ON  ANGIOGENESIS+PFT,OLD,NT/CT
L26              QUE  ABB=ON  PLU=ON  "CARDIOVASCULAR SYSTEM, DISEASE"+PFT
                 ,OLD,NT/CT
L27              QUE  ABB=ON  PLU=ON  CERAMIDES+PFT,OLD,NT/CT
L28              QUE  ABB=ON  PLU=ON  SPHINGOMYELINS+PFT,OLD,NT/CT
L29              QUE  ABB=ON  PLU=ON  "ENZYMES, BIOLOGICAL STUDIES"+PFT,OL
                 D,NT/CT
L30              QUE  ABB=ON  PLU=ON  ENZYMES+PFT,OLD/CT
L31              QUE  ABB=ON  PLU=ON  SPHINGOLIPIDS+PFT,OLD,NT/CT
L32              QUE  ABB=ON  PLU=ON  SPHINGOSINES+PFT,OLD,NT/CT
L33              QUE  ABB=ON  PLU=ON  ALTER OR ALTERS OR ALTERED OR ALTERI
                 NG OR MODERAT? OR MODULAT? OR REGULAT? OR CONTROL? OR MED
                 IAT?
L34              QUE  ABB=ON  PLU=ON  IMPED? OR REDUC? OR DEPRESS? OR REPR
                 ESS? OR SUPPRESS? OR INHIBIT? OR PROHIBIT? OR ANTAGON? OR
                  PREVENT? OR INTERRUPT? OR DISRUPT? OR RETARD? OR SLOW? O
                 R BLOCK? OR TERMINAT? OR RESTRICT? OR STOP?
L35              QUE  ABB=ON  PLU=ON  AGON? OR PROMOT? OR ELICIT? OR ENCOU
                 RAG? OR STIMULAT? OR CAUSE OR CAUSED OR CAUSES OR CAUSING
                  OR EFFECTS OR EFFECTED OR EFFECTING OR EFFECT OR ENHANC?
                  OR AMPLIF? OR ACCELERAT?
L38              QUE  ABB=ON  PLU=ON  ENZYM?/CW
L41              QUE  ABB=ON  PLU=ON  ?SPHINGO?
L45              QUE  ABB=ON  PLU=ON  "ARTERY, DISEASE"+PFT,OLD,NT/CT
L46              QUE  ABB=ON  PLU=ON  INDUC?
L59          721 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L19 OR (L20 OR L21 OR L22 OR
                 L23 OR L24 OR L25 OR L26) OR L45)(L) (L10 OR L11 OR L41)
L60         7098 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L27 OR L28 OR (L31 OR L32)
                 OR (?SPHINGO?/CW))(L) ((L12 OR L13 OR L14 OR L15))
L61          738 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ((L29 OR L30) OR L38)(L)(L41
                 OR L10 OR L11)
L62          263 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L59 AND ((L60 OR L61))
L63          180 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L62 AND L7
L64        10303 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L33 OR L34 OR L35 OR
                 L46)(10A) L41
L65           62 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L63 AND L64
L66           55 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L63 AND L4
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L67          77 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L65 OR L66
L70             QUE  ABB=ON  PLU=ON  TREAT? OR ?THERAP? OR MEDIC? OR PHAR
                M?
L71             QUE  ABB=ON  PLU=ON  PREVENT? OR AVOID?
L72             QUE  ABB=ON  PLU=ON  ADMIN?
L73          26 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L67 AND ((L70 OR L71 OR L72))

L76          26 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L73 AND L41
L78          26 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L73 OR L76


=> d que stat l97
L8              QUE  ABB=ON  PLU=ON  AY<2001 OR PY<2001 OR PRY<2001
L81             QUE  ABB=ON  PLU=ON  (B14-F? OR C14-F?)/MC
L82         472 SEA FILE=WPIX ABB=ON  PLU=ON  ((ALTER/BIX OR ALTERS/BIX OR
                ALTERED/BIX OR ALTERING/BIX OR MODERAT?/BIX OR MODULAT?/BIX OR
                REGULAT?/BIX OR CONTROL?/BIX OR MEDIAT?/BIX) OR (IMPED?/BIX OR
                REDUC?/BIX OR DEPRESS?/BIX OR REPRESS?/BIX OR SUPPRESS?/BIX OR
                INHIBIT?/BIX OR PROHIBIT?/BIX OR ANTAGON?/BIX OR PREVENT?/BIX
                OR INTERRUPT?/BIX OR DISRUPT?/BIX OR RETARD?/BIX OR SLOW?/BIX
                OR BLOCK?/BIX OR TERMINAT?/BIX OR RESTRICT?/BIX OR STOP?/BIX)
                OR (INDUC?/BIX))(15A)((?SPHINGO?/BIX) OR (SMASE/BIX) OR
                (SPHINGOMYELINAS?/BIX))
L86             QUE  ABB=ON  PLU=ON  C12N009/IPC
L89             QUE  ABB=ON  PLU=ON  A61P?/IPC
L90         238 SEA FILE=WPIX ABB=ON  PLU=ON  L82 AND L8
L91          41 SEA FILE=WPIX ABB=ON  PLU=ON  L90 AND L86
L92          88 SEA FILE=WPIX ABB=ON  PLU=ON  L90 AND (L81 OR L89)
L93          22 SEA FILE=WPIX ABB=ON  PLU=ON  L91 AND L92
L95          16 SEA FILE=WPIX ABB=ON  PLU=ON  L93 AND ((HEART?/BIX OR ?CORONAR?
                /BIX OR ?CARDIO?/BIX OR ?CARDIA?/BIX OR MYOCARD?/BIX) OR
                (ISCHEM?/BIX OR POSTISCHEM?/BIX OR REPERFUS?/BIX OR NEOVASCUL?/
                BIX OR (NEO/BIX(W)VASCUL?/BIX) OR ANGIOGEN?/BIX OR (ANGIO/BIX(W
                )GENE?/BIX) OR STENT?/BIX OR ?STENOSIS?/BIX OR RESTENOSIS?/BIX
                OR STROKE?/BIX) OR (?CEREBR?/BIX OR BRAIN/BIX) OR (VASCU?/BIX
                OR VEIN?/BIX OR ARTER?/BIX))
L96          22 SEA FILE=WPIX ABB=ON  PLU=ON  L93 AND (?SPHINGO?/BIX OR
                (SMASE/BIX) OR (SPHINGOMYELINAS?/BIX) OR (?SPHINGO?/BIX OR
                ?CERAMID?/BIX OR KETOSPHING?/BIX OR GALACTOSYLCERAMID?/BIX OR
                DIHYDROCERAMID?/BIX) OR (CEREBROSID?/BIX OR ?PALMITOYLTRANSFER?
                /BIX OR (?PALMITOYL?/BIX(1A)TRANSFERAS?/BIX) OR (NADPH/BIX(3A)R
                EDUCTAS?/BIX)))
L97          22 SEA FILE=WPIX ABB=ON  PLU=ON  L93 OR L95 OR L96


=> d que stat l119
L1            1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  US2001-29372/APPS
L3              TRANSFER  PLU=ON  L1 1- RN :      24 TERMS
L4           24 SEA FILE=REGISTRY ABB=ON  PLU=ON  L3
L7              QUE  ABB=ON  PLU=ON  AY<2001 OR PY<2001 OR PRY<2001 OR MY
                <2001 OR REVIEW/DT
L10             QUE  ABB=ON  PLU=ON  ?SPHINGO? OR ?CERAMID? OR KETOSPHING
                ? OR GALACTOSYLCERAMID? OR DIHYDROCERAMID?
L11             QUE  ABB=ON  PLU=ON  CEREBROSID? OR ?PALMITOYLTRANSFER? O
                R (?PALMITOYL?(1A)TRANSFERAS?) OR (NADPH(3A)REDUCTAS?)
L12             QUE  ABB=ON  PLU=ON  HEART? OR ?CORONAR? OR ?CARDIO? OR ?
                CARDIA? OR MYOCARD?
L13             QUE  ABB=ON  PLU=ON  ISCHEM? OR POSTISCHEM? OR REPERFUS?
                OR NEOVASCUL? OR (NEO(W)VASCUL?) OR ANGIOGEN? OR (ANGIO(W
                )GENE?) OR STENT? OR ?STENOSIS? OR RESTENOSIS? OR STROKE?
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L14             QUE  ABB=ON  PLU=ON  ?CEREBR? OR BRAIN
L15             QUE  ABB=ON  PLU=ON  VASCU? OR VEIN? OR ARTER?
L33             QUE  ABB=ON  PLU=ON  ALTER OR ALTERS OR ALTERED OR ALTERI
                NG OR MODERAT? OR MODULAT? OR REGULAT? OR CONTROL? OR MED
                IAT?
L34             QUE  ABB=ON  PLU=ON  IMPED? OR REDUC? OR DEPRESS? OR REPR
                ESS? OR SUPPRESS? OR INHIBIT? OR PROHIBIT? OR ANTAGON? OR
                 PREVENT? OR INTERRUPT? OR DISRUPT? OR RETARD? OR SLOW? O
                R BLOCK? OR TERMINAT? OR RESTRICT? OR STOP?
L35             QUE  ABB=ON  PLU=ON  AGON? OR PROMOT? OR ELICIT? OR ENCOU
                RAG? OR STIMULAT? OR CAUSE OR CAUSED OR CAUSES OR CAUSING
                 OR EFFECTS OR EFFECTED OR EFFECTING OR EFFECT OR ENHANC?
                 OR AMPLIF? OR ACCELERAT?
L41             QUE  ABB=ON  PLU=ON  ?SPHINGO?
L46             QUE  ABB=ON  PLU=ON  INDUC?
L70             QUE  ABB=ON  PLU=ON  TREAT? OR ?THERAP? OR MEDIC? OR PHAR
                M?
L71             QUE  ABB=ON  PLU=ON  PREVENT? OR AVOID?
L72             QUE  ABB=ON  PLU=ON  ADMIN?
L79             QUE  ABB=ON  PLU=ON  SMASE
L80             QUE  ABB=ON  PLU=ON  SPHINGOMYELINAS?
L101            QUE  ABB=ON  PLU=ON  SPHINGOLIPIDS+PFT,OLD,NT/CT
L102      16230 SEA FILE=MEDLINE ABB=ON  PLU=ON  (L33 OR L34 OR L35 OR
                L46)(10A)(L41 OR L79 OR L80 OR L10 OR L11 OR ?SPHINGO?)
L103     354457 SEA FILE=MEDLINE ABB=ON  PLU=ON  (L70 OR L71 OR L72) (10A)(L12
                OR L13 OR L14 OR L15)
L104        360 SEA FILE=MEDLINE ABB=ON  PLU=ON  L102 AND L103
L105        217 SEA FILE=MEDLINE ABB=ON  PLU=ON  L104 AND L7
L106         25 SEA FILE=MEDLINE ABB=ON  PLU=ON  L105 AND L4
L107         82 SEA FILE=MEDLINE ABB=ON  PLU=ON  L105 AND (L101 OR ((?SPHINGO?/
                TI,IT,CC,CT,ST,STP) OR (SMASE/TI,IT,CC,CT,ST,STP) OR (SPHINGOMY
                ELINAS?/TI,IT,CC,CT,ST,STP)))
L108         82 SEA FILE=MEDLINE ABB=ON  PLU=ON  L106 OR L107
L111         77 SEA FILE=MEDLINE ABB=ON  PLU=ON  L108 AND ((L10 OR L11 OR L41
                OR L79 OR L80)(L)(L72 OR L70))
L112         28 SEA FILE=MEDLINE ABB=ON  PLU=ON  L108 AND ((L12 OR L13 OR L14
                OR L15)(L)(DE OR DT))
L113         27 SEA FILE=MEDLINE ABB=ON  PLU=ON  L111 AND L112
L114         28 SEA FILE=MEDLINE ABB=ON  PLU=ON  (L112 OR L113)
L117         41 SEA FILE=MEDLINE ABB=ON  PLU=ON  L114 OR L106
L118         22 SEA FILE=MEDLINE ABB=ON  PLU=ON  L117 AND L101
L119         31 SEA FILE=MEDLINE ABB=ON  PLU=ON  L114 OR L118


=> d que stat l140
L1            1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  US2001-29372/APPS
L3              TRANSFER  PLU=ON  L1 1- RN :      24 TERMS
L4           24 SEA FILE=REGISTRY ABB=ON  PLU=ON  L3
L7              QUE  ABB=ON  PLU=ON  AY<2001 OR PY<2001 OR PRY<2001 OR MY
                <2001 OR REVIEW/DT
L10             QUE  ABB=ON  PLU=ON  ?SPHINGO? OR ?CERAMID? OR KETOSPHING
                ? OR GALACTOSYLCERAMID? OR DIHYDROCERAMID?
L11             QUE  ABB=ON  PLU=ON  CEREBROSID? OR ?PALMITOYLTRANSFER? O
                R (?PALMITOYL?(1A)TRANSFERAS?) OR (NADPH(3A)REDUCTAS?)
L12             QUE  ABB=ON  PLU=ON  HEART? OR ?CORONAR? OR ?CARDIO? OR ?
                CARDIA? OR MYOCARD?
L13             QUE  ABB=ON  PLU=ON  ISCHEM? OR POSTISCHEM? OR REPERFUS?
                OR NEOVASCUL? OR (NEO(W)VASCUL?) OR ANGIOGEN? OR (ANGIO(W
                )GENE?) OR STENT? OR ?STENOSIS? OR RESTENOSIS? OR STROKE?
L14             QUE  ABB=ON  PLU=ON  ?CEREBR? OR BRAIN
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L33             QUE  ABB=ON  PLU=ON  ALTER OR ALTERS OR ALTERED OR ALTERI
                NG OR MODERAT? OR MODULAT? OR REGULAT? OR CONTROL? OR MED
                IAT?
L34             QUE  ABB=ON  PLU=ON  IMPED? OR REDUC? OR DEPRESS? OR REPR
                ESS? OR SUPPRESS? OR INHIBIT? OR PROHIBIT? OR ANTAGON? OR
                 PREVENT? OR INTERRUPT? OR DISRUPT? OR RETARD? OR SLOW? O
                R BLOCK? OR TERMINAT? OR RESTRICT? OR STOP?
L35             QUE  ABB=ON  PLU=ON  AGON? OR PROMOT? OR ELICIT? OR ENCOU
                RAG? OR STIMULAT? OR CAUSE OR CAUSED OR CAUSES OR CAUSING
                 OR EFFECTS OR EFFECTED OR EFFECTING OR EFFECT OR ENHANC?
                 OR AMPLIF? OR ACCELERAT?
L41             QUE  ABB=ON  PLU=ON  ?SPHINGO?
L46             QUE  ABB=ON  PLU=ON  INDUC?
L70             QUE  ABB=ON  PLU=ON  TREAT? OR ?THERAP? OR MEDIC? OR PHAR
                M?
L71             QUE  ABB=ON  PLU=ON  PREVENT? OR AVOID?
L72             QUE  ABB=ON  PLU=ON  ADMIN?
L79             QUE  ABB=ON  PLU=ON  SMASE
L80             QUE  ABB=ON  PLU=ON  SPHINGOMYELINAS?
L125            QUE  ABB=ON  PLU=ON  INJUR?
L126      13187 SEA FILE=EMBASE ABB=ON  PLU=ON  (L33 OR L34 OR L35 OR L46)(10A)
                (L10 OR L11 OR L41 OR L79 OR L80)
L127      62033 SEA FILE=EMBASE ABB=ON  PLU=ON  ((L70 OR L71 OR L72))(10A)L13
L128       5359 SEA FILE=EMBASE ABB=ON  PLU=ON  ((L70 OR L71 OR L72))(10A)((L12
                 OR L14)(10A)L125)
L129         55 SEA FILE=EMBASE ABB=ON  PLU=ON  L126 AND (L127 OR L128)
L130        103 SEA FILE=EMBASE ABB=ON  PLU=ON  (L127 OR L128) AND L4
L131         75 SEA FILE=EMBASE ABB=ON  PLU=ON  (L129 OR L130) AND L7
L132            QUE  ABB=ON  PLU=ON  ?ISCHAEM?
L133         15 SEA FILE=EMBASE ABB=ON  PLU=ON  L126 AND L132
L134         87 SEA FILE=EMBASE ABB=ON  PLU=ON  L131 OR L133
L135         79 SEA FILE=EMBASE ABB=ON  PLU=ON  L134 AND L7
L136         10 SEA FILE=EMBASE ABB=ON  PLU=ON  L135 AND (L41 OR L79 OR L80)
L138        101 SEA FILE=EMBASE ABB=ON  PLU=ON  (L127 OR L128) AND (L41 OR L79
                OR L80 OR L10 OR L11)
L139         41 SEA FILE=EMBASE ABB=ON  PLU=ON  L138 AND L7
L140         43 SEA FILE=EMBASE ABB=ON  PLU=ON  L136 OR L139


=> d que stat l148
L1            1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  US2001-29372/APPS
L3              TRANSFER  PLU=ON  L1 1- RN :      24 TERMS
L4           24 SEA FILE=REGISTRY ABB=ON  PLU=ON  L3
L7              QUE  ABB=ON  PLU=ON  AY<2001 OR PY<2001 OR PRY<2001 OR MY
                <2001 OR REVIEW/DT
L12             QUE  ABB=ON  PLU=ON  HEART? OR ?CORONAR? OR ?CARDIO? OR ?
                CARDIA? OR MYOCARD?
L13             QUE  ABB=ON  PLU=ON  ISCHEM? OR POSTISCHEM? OR REPERFUS?
                OR NEOVASCUL? OR (NEO(W)VASCUL?) OR ANGIOGEN? OR (ANGIO(W
                )GENE?) OR STENT? OR ?STENOSIS? OR RESTENOSIS? OR STROKE?
L14             QUE  ABB=ON  PLU=ON  ?CEREBR? OR BRAIN
L70             QUE  ABB=ON  PLU=ON  TREAT? OR ?THERAP? OR MEDIC? OR PHAR
                M?
L71             QUE  ABB=ON  PLU=ON  PREVENT? OR AVOID?
L72             QUE  ABB=ON  PLU=ON  ADMIN?
L125            QUE  ABB=ON  PLU=ON  INJUR?
L132            QUE  ABB=ON  PLU=ON  ?ISCHAEM?
L141      73704 SEA FILE=BIOSIS ABB=ON  PLU=ON  (L70 OR L71 OR L72)(15A)(L132
                OR L13)
L142       5560 SEA FILE=BIOSIS ABB=ON  PLU=ON  (L70 OR L71 OR L72)(15A)((L12
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                OR L14)(7A)L125)
L146          23 SEA FILE=REGISTRY ABB=ON  PLU=ON  L4 NOT GENTAMICIN/CN
L147          23 SEA FILE=BIOSIS ABB=ON  PLU=ON  (L141 OR L142) AND L146
L148           2 SEA FILE=BIOSIS ABB=ON  PLU=ON  L147 AND L7


=> d his l157

     (FILE 'BIOSIS, PASCAL, JICST-EPLUS, CABA, LIFESCI, BIOENG, BIOTECHNO,
     BIOTECHDS, DRUGU, DRUGB, VETU, VETB, SCISEARCH, CONFSCI, DISSABS' ENTERED
     AT 13:22:58 ON 11 JUL 2006)
L157          35 S L156 AND (L41 OR L79 OR L80)

=> d que stat l157
L1             1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  US2001-29372/APPS
L3               TRANSFER  PLU=ON  L1 1- RN :      24 TERMS
L4            24 SEA FILE=REGISTRY ABB=ON  PLU=ON  L3
L7               QUE  ABB=ON  PLU=ON  AY<2001 OR PY<2001 OR PRY<2001 OR MY
                 <2001 OR REVIEW/DT
L10              QUE  ABB=ON  PLU=ON  ?SPHINGO? OR ?CERAMID? OR KETOSPHING
                 ? OR GALACTOSYLCERAMID? OR DIHYDROCERAMID?
L11              QUE  ABB=ON  PLU=ON  CEREBROSID? OR ?PALMITOYLTRANSFER? O
                 R (?PALMITOYL?(1A)TRANSFERAS?) OR (NADPH(3A)REDUCTAS?)
L12              QUE  ABB=ON  PLU=ON  HEART? OR ?CORONAR? OR ?CARDIO? OR ?
                 CARDIA? OR MYOCARD?
L13              QUE  ABB=ON  PLU=ON  ISCHEM? OR POSTISCHEM? OR REPERFUS?
                 OR NEOVASCUL? OR (NEO(W)VASCUL?) OR ANGIOGEN? OR (ANGIO(W
                 )GENE?) OR STENT? OR ?STENOSIS? OR RESTENOSIS? OR STROKE?
L14              QUE  ABB=ON  PLU=ON  ?CEREBR? OR BRAIN
L33              QUE  ABB=ON  PLU=ON  ALTER OR ALTERS OR ALTERED OR ALTERI
                 NG OR MODERAT? OR MODULAT? OR REGULAT? OR CONTROL? OR MED
                 IAT?
L34              QUE  ABB=ON  PLU=ON  IMPED? OR REDUC? OR DEPRESS? OR REPR
                 ESS? OR SUPPRESS? OR INHIBIT? OR PROHIBIT? OR ANTAGON? OR
                  PREVENT? OR INTERRUPT? OR DISRUPT? OR RETARD? OR SLOW? O
                 R BLOCK? OR TERMINAT? OR RESTRICT? OR STOP?
L35              QUE  ABB=ON  PLU=ON  AGON? OR PROMOT? OR ELICIT? OR ENCOU
                 RAG? OR STIMULAT? OR CAUSE OR CAUSED OR CAUSES OR CAUSING
                  OR EFFECTS OR EFFECTED OR EFFECTING OR EFFECT OR ENHANC?
                  OR AMPLIF? OR ACCELERAT?
L41              QUE  ABB=ON  PLU=ON  ?SPHINGO?
L46              QUE  ABB=ON  PLU=ON  INDUC?
L70              QUE  ABB=ON  PLU=ON  TREAT? OR ?THERAP? OR MEDIC? OR PHAR
                 M?
L71              QUE  ABB=ON  PLU=ON  PREVENT? OR AVOID?
L79              QUE  ABB=ON  PLU=ON  SMASE
L80              QUE  ABB=ON  PLU=ON  SPHINGOMYELINAS?
L125             QUE  ABB=ON  PLU=ON  INJUR?
L132             QUE  ABB=ON  PLU=ON  ?ISCHAEM?
L146          23 SEA FILE=REGISTRY ABB=ON  PLU=ON  L4 NOT GENTAMICIN/CN
L149       58726 SEA (L33 OR L34 OR L35 OR L46)(15A)(L10 OR L11 OR L41 OR L79
                 OR L80)
L150      199405 SEA (L70 OR L71) (10A)(L13 OR L132)
L151       14817 SEA (L70 OR L71) (10A)((L12 OR L14)(10A) L125)
L152         261 SEA L149 AND (L150 OR L151)
L153             SEL  PLU=ON  L146 1- CHEM :      123 TERMS
L154       49231 SEA L153
L155         137 SEA (L150 OR L151) AND L154
L156         103 SEA (L152 OR L155) AND L7
L157          35 SEA L156 AND (L41 OR L79 OR L80)
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=> dup rem l78 l97 l119 l140 l148 l157
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FILE 'SCISEARCH' ENTERED AT 13:45:32 ON 11 JUL 2006
Copyright (c) 2006 The Thomson Corporation
PROCESSING COMPLETED FOR L78
PROCESSING COMPLETED FOR L97
PROCESSING COMPLETED FOR L119
PROCESSING COMPLETED FOR L140
PROCESSING COMPLETED FOR L148
PROCESSING COMPLETED FOR L157
L161        127 DUP REM L78 L97 L119 L140 L148 L157 (32 DUPLICATES REMOVED)
                ANSWERS '1-26' FROM FILE HCAPLUS
                ANSWERS '27-47' FROM FILE WPIX
                ANSWERS '48-75' FROM FILE MEDLINE
                ANSWERS '76-113' FROM FILE EMBASE
                ANSWER '114' FROM FILE PASCAL
                ANSWERS '115-116' FROM FILE LIFESCI
                ANSWER '117' FROM FILE BIOENG
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ANSWERS '118-120' FROM FILE BIOTECHDS
ANSWERS '121-124' FROM FILE DRUGU
ANSWERS '125-127' FROM FILE SCISEARCH

=> file stnguide
FILE 'STNGUIDE' ENTERED AT 13:45:50 ON 11 JUL 2006

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jul 7, 2006 (20060707/UP).

=> d ibib ed ab hitind hitstr
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, PASCAL, LIFESCI, BIOENG, BIOTECHDS, DRUGU, SCISEARCH' - CONTINUE? (Y)/N:y

L161 ANSWER 1 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2006:145909 HCAPLUS
DOCUMENT NUMBER: 144:205012
TITLE: **Sphingosine** 1-phosphate in vascular biology: possible **therapeutic** strategies to **control** vascular diseases
AUTHOR(S): Yatomi, Y.
CORPORATE SOURCE: Department of Laboratory Medicine, Graduate School of Medicine, University of Tokyo, Tokyo, Japan
SOURCE: Current Pharmaceutical Design (2006), 12(5), 575-587
CODEN: CPDEFP; ISSN: 1381-6128
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
ED Entered STN: 16 Feb 2006
AB A review. Blood platelets are very unique in that they store **sphingosine** 1-phosphate (Sph-1-P) abundantly (possibly due to the existence of highly active **sphingosine** kinase and a lack of Sph-1-P lyase) and release this bioactive lipid extracellularly upon stimulation. Vascular endothelial cells (ECs) and smooth muscle cells (SMCs) respond dramatically to this platelet-derived bioactive lipid mainly through a family of G protein-coupled Sph-1-P receptors named S1P1, 2, 3, 4, and 5, originally referred to as EDG-1, 5, 3, 6, and 8, resp. In fact, the importance of Sph-1-P in platelet-vascular cell interactions has been revealed in a number of recent reports. Through interaction with ECs, Sph-1-P can mediate physiol. wound healing processes such as vascular repair, although this important bioactive lipid can become atherogenic and thrombogenic, and cause or aggravate cardiovascular diseases especially under certain pathol. conditions. Sph-1-P induces vasoconstriction through interaction with SMCs. It is likely that regulation of Sph-1-P biol. activities is important for the **therapeutical** purpose to control vascular disorders. Particularly, the development of specific S1P receptor agonists or antagonists seems a reasonable strategy to selectively regulate the bioactivity of Sph-1-P, considering that a great diversity of Sph-1-P actions has been reported and that this diversity depends mainly on the S1P receptor subtype involved. In this review, I will summarize recent findings on possible roles of Sph-1-P in vascular biol. and its **therapeutical** implications.
CC 1-0 (Pharmacology)
ST review **sphingosine** phosphate vascular disease atherosclerosis **therapy**
IT Antiarteriosclerotics
(antiatherosclerotics; **sphingosine** phosphate and possible **therapeutic** strategies to **control** vascular diseases)
IT **Ischemia**
(cardiac; **sphingosine** phosphate and possible **therapeutic** strategies to **control** vascular diseases)
IT **Artery, disease**
(cerebral, spasm; **sphingosine** phosphate and possible **therapeutic** strategies to **control** vascular diseases)
IT **Heart, disease**
(ischemia; **sphingosine** phosphate and possible **therapeutic** strategies to **control** vascular diseases)
IT **Angiogenesis**

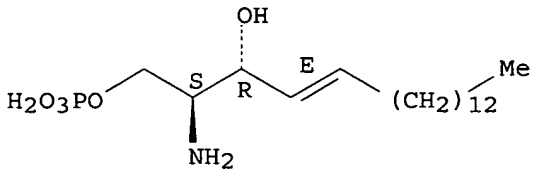
Atherosclerosis
Blood vessel, disease
(**sphingosine** phosphate and possible **therapeutic** strategies to **control** vascular diseases)

IT **26993-30-6**, **Sphingosine** 1-phosphate
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**sphingosine** phosphate and possible **therapeutic** strategies to **control vascular** diseases)

IT **26993-30-6**, **Sphingosine** 1-phosphate
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**sphingosine** phosphate and possible **therapeutic** strategies to **control vascular** diseases)

RN 26993-30-6 HCAPLUS
CN 4-Octadecene-1,3-diol, 2-amino-, 1-(dihydrogen phosphate), (2S,3R,4E)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



REFERENCE COUNT: 115 THERE ARE 115 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, PASCAL, LIFESCI, BIOENG, BIOTECHDS, DRUGU, SCISEARCH' - CONTINUE? (Y)/N:y

L161 ANSWER 2 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2002:504646 HCAPLUS
DOCUMENT NUMBER: 137:83610
TITLE: Compositions and methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor
INVENTOR(S): Sabbadini, Roger A.
PATENT ASSIGNEE(S): Medlyte, Inc., USA
SOURCE: PCT Int. Appl., 188 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002051439	A2	20020704	WO 2001-US50785	20011221 <--
WO 2002051439	A3	20030814		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB,
GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2432978	AA	20020704	CA 2001-2432978		20011221 <--
US 2003026799	A1	20030206	US 2001-28156		20011221 <--
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US 2003027304	A1	20030206	US 2001-29401		20011221 <--
US 6858383	B2	20050222			
US 2003096022	A1	20030522	US 2001-29372		20011221 <--
EP 1363643	A2	20031126	EP 2001-987517		20011221 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
US 2004247603	A1	20041209	US 2004-820582		20040407 <--
US 2005226862	A1	20051013	US 2005-101976		20050407 <--
PRIORITY APPLN. INFO.:			US 2000-257926P	P	20001222 <--
			US 2001-28156	A3	20011221
			WO 2001-US50785	W	20011221

OTHER SOURCE(S): MARPAT 137:83610
ED Entered STN: 05 Jul 2002
AB Methods and compns. are disclosed that are useful for the **prevention** and/or **treatment** of cardiovascular and cardiac diseases and disorders, or damage resulting from surgical or **medical** procedures that may cause ischemic or ischemic/reperfusion damage in humans; and cardiovascular trauma. The beneficial effects of the compns. and methods are achieved through the use of **pharmaceutical** compns. that include agents that interfere with the production and/or biol. activities of **sphingolipids** and their metabolites, particularly **sphingosine** (SPH) and **sphingosine**-1-phosphate (S-1-P). Also disclosed are methods for identifying and isolating **therapeutic** agents.
IC ICM A61K039-395
CC 63-3 (Pharmaceuticals)
Section cross-reference(s): 1, 15
ST **sphingolipid** metab cardiovascular disease drug screening
IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(AXOR29; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)
IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Edg-1; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)
IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Edg-3; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)
IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Edg-5; **sphingosine** metabolism in relation to methods for the

treatment and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study) (Edg-6; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study) (Edg-8; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study) (Mil; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study) (NRG1; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT Gene, animal
Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study) (SCaMPER; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT Glycosides
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(amino, library; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT Artery
Surgery
(angioplasty; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT Nucleic acids
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aptamers; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT Drug delivery systems
Ischemia
(cardiac; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT **Ischemia**

(cerebral; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT **Surgery**
(coronary artery bypass; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT Artery
(coronary, bypass surgery; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT **Artery, disease**
(coronary; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT **Ceramides**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(dihydro; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of **cardiovascular** diseases and disorders, and for identifying agents **therapeutic** therefor)

IT High throughput screening
(drug; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT **Sphingomyelins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(enzymes metabolizing; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of **cardiovascular** diseases and disorders, and for identifying agents **therapeutic** therefor)

IT **Heart, disease**
(failure, idiopathic; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT **Heart, disease**
(failure; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(for **sphingolipids**; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT Drug screening
(high throughput; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT **Heart, disease**
(infarction; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular

diseases and disorders, and for identifying agents **therapeutic** therefor)

IT **Reperfusion**
(injury; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT **Brain, disease**
Heart, disease
(ischemia; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT Antibodies and Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monoclonal; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT **Angiogenesis**
(neovascularization; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT Injury
(reperfusion; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT Antibodies and Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(single chain; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT mRNA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**sphingolipid**-metabolizing enzyme-encoding; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT **Enzymes, biological studies**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**sphingolipid**-metabolizing; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT Animal tissue culture
Cardiovascular system, disease
Combinatorial library
Drug screening
Gene **therapy**
Genetic vectors
Heart, disease
Heart, disease
Human
Molecular cloning
Rattus

Signal transduction, biological
cDNA sequences
(**sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT Cytokines
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT **Sphingolipids**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of **cardiovascular** diseases and disorders, and for identifying agents **therapeutic** therefor)

IT **Sphingosines**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of **cardiovascular** diseases and disorders, and for identifying agents **therapeutic** therefor)

IT Antibodies and Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT Antisense oligonucleotides
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT Oligonucleotides
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT **Medical** goods
(stents; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT Brain
(vascular disease of; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT **85305-88-0**, Galactosylceramide
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(enzyme producing; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of **cardiovascular** diseases and disorders, and for identifying agents **therapeutic** therefor)

IT **440004-01-3**, DNA (rat gene SCaMPER protein cDNA)
440004-02-4, DNA (human gene SCaMPER protein cDNA)

440004-03-5, DNA (rat gene Edg-3 receptor cDNA)
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT **123-78-4**, **Sphingosine** **764-22-7**, Sphinganine
18944-28-0, 3-Ketosphinganine **26993-30-6**,
Sphingosine 1 phosphate **56467-83-5**, Ceramidase
62213-50-7, Serine palmitoyltransferase **123175-68-8**,
Ceramide kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of **cardiovascular** diseases and disorders, and for identifying agents **therapeutic** therefor)

IT **9031-54-3**, **Sphingomyelinase** **9055-50-9**, Nadph
reductase **37257-09-3**, Ceramide synthase
50864-48-7, **Sphingosine** kinase **58703-97-2**,
Sphingomyelin synthase **103843-28-3**, Desaturase
169277-44-5, **Sphingosine**-1-phosphate phosphatase
179241-79-3, **Sphingomyelin** deacylase
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT **1403-66-3D**, Gentamicin, derivs.
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT **440075-36-5** **440075-37-6** **440075-38-7**
440075-39-8
RL: PRP (Properties)
(unclaimed nucleotide sequence; compns. and methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)

IT **85305-88-0**, Galactosylceramide
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(enzyme producing; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of **cardiovascular** diseases and disorders, and for identifying agents **therapeutic** therefor)

RN 85305-88-0 HCAPLUS
CN Ceramide, 1-O-β-D-galactopyranosyl- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **440004-01-3**, DNA (rat gene SCaMPER protein cDNA)
440004-02-4, DNA (human gene SCaMPER protein cDNA)
440004-03-5, DNA (rat gene Edg-3 receptor cDNA)
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; **sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents

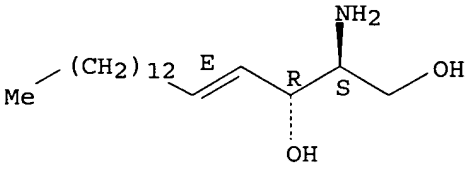
therapeutic therefor)
RN 440004-01-3 HCAPLUS
CN DNA (rat gene SCaMPER protein cDNA) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 440004-02-4 HCAPLUS
CN DNA (human gene SCaMPER protein cDNA) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 440004-03-5 HCAPLUS
CN DNA (rat gene Edg-3 receptor cDNA) (9CI) (CA INDEX NAME)

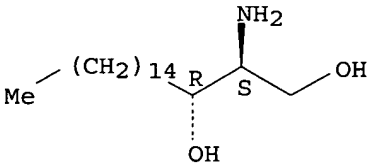
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **123-78-4**, **Sphingosine 764-22-7**, Sphinganine
18944-28-0, 3-Ketosphinganine **26993-30-6**,
Sphingosine 1 phosphate **56467-83-5**, Ceramidase
62213-50-7, Serine palmitoyltransferase **123175-68-8**,
Ceramide kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**sphingosine** metabolism in relation to methods for the
treatment and **prevention** of **cardiovascular**
diseases and disorders, and for identifying agents **therapeutic**
therefor)
RN 123-78-4 HCAPLUS
CN 4-Octadecene-1,3-diol, 2-amino-, (2S,3R,4E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



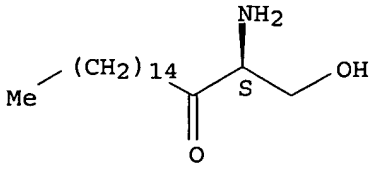
RN 764-22-7 HCAPLUS
CN 1,3-Octadecanediol, 2-amino-, (2S,3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



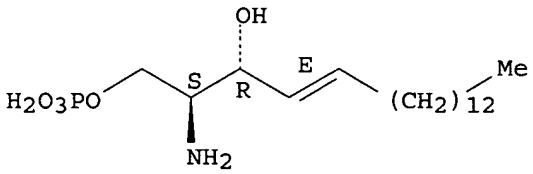
RN 18944-28-0 HCAPLUS
CN 3-Octadecanone, 2-amino-1-hydroxy-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 26993-30-6 HCAPLUS
CN 4-Octadecene-1,3-diol, 2-amino-, 1-(dihydrogen phosphate), (2S,3R,4E)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



RN 56467-83-5 HCAPLUS
CN Ceramidase (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 62213-50-7 HCAPLUS
CN Palmitoyltransferase, serine (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 123175-68-8 HCAPLUS
CN Kinase (phosphorylating), acylsphingosine (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **9031-54-3**, **Sphingomyelinase 9055-50-9**, Nadph **reductase 37257-09-3**, Ceramide synthase **50864-48-7**, **Sphingosine** kinase **58703-97-2**, **Sphingomyelin** synthase **103843-28-3**, Desaturase **169277-44-5**, **Sphingosine**-1-phosphate phosphatase **179241-79-3**, **Sphingomyelin** deacylase
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)
RN 9031-54-3 HCAPLUS
CN Sphingomyelinase C (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9055-50-9 HCAPLUS
CN Reductase, reduced nicotinamide adenine dinucleotide phosphate (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 37257-09-3 HCAPLUS
CN Acyltransferase, sphingosine (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 50864-48-7 HCAPLUS
CN Kinase (phosphorylating), dihydrosphingosine (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 58703-97-2 HCAPLUS
CN Cholinephosphotransferase, phosphatidylcholine-ceramide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 103843-28-3 HCAPLUS
CN Desaturase (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 169277-44-5 HCAPLUS
CN Phosphatase, sphingosine phosphate (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 179241-79-3 HCAPLUS
CN Amidase, sphingomyelin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **1403-66-3D**, Gentamicin, derivs.
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**sphingosine** metabolism in relation to methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)
RN 1403-66-3 HCAPLUS
CN Gentamicin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **440075-36-5 440075-37-6 440075-38-7 440075-39-8**
RL: PRP (Properties)
(unclaimed nucleotide sequence; compns. and methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor)
RN 440075-36-5 HCAPLUS
CN DNA, d(C-C-A-G-G-A-T-T-C-A-T-C-A-T-A-T-G-T-T-A-A-A-G) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 440075-37-6 HCAPLUS
CN DNA, d(A-T-C-A-G-T-G-G-G-T-G-C-A-T-C-A-G-T-A-G-C) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 440075-38-7 HCAPLUS
CN DNA, d(T-T-A-T-G-G-C-A-A-C-C-A-C-G-C-A-C-G-C-G-C-A-G-G) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 440075-39-8 HCAPLUS
CN DNA, d(A-G-A-C-C-G-T-C-A-C-T-T-G-C-A-G-A-G-G-A-C) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L161 ANSWER 3 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 2001:125933 HCAPLUS

DOCUMENT NUMBER: 134:293995
TITLE: Pivotal role for acidic **sphingomyelinase** in cerebral ischemia-**induced** ceramide and cytokine production, and neuronal apoptosis
AUTHOR(S): Yu, Zai Fang; Nikolova-Karakashian, Mariana; Zhou, Daohong; Cheng, Guanjun; Schuchman, Edward H.; Mattson, Mark P.
CORPORATE SOURCE: Sanders-Brown Research Center on Aging, University of Kentucky, Lexington, KY, 40536, USA
SOURCE: Journal of Molecular Neuroscience (**2000**), 15(2), 85-97
CODEN: JMNEES; ISSN: 0895-8696
PUBLISHER: Humana Press Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 21 Feb 2001
AB Stroke is a major cause of long-term disability, the severity of which is directly related to the nos. of neurons that succumb to the ischemic insult. The signaling cascades activated by cerebral ischemia that may either promote or protect against neuronal death are not well-understood. One injury-responsive signaling pathway that has recently been characterized in studies of non-neural cells involves cleavage of membrane **sphingomyelin** by acidic and/or neutral **sphingomyelinase** (ASMase) resulting in generation of the second messenger ceramide. Here,transient focal cerebral ischemia induced large increases in ASMase activity, ceramide levels, and production of inflammatory cytokines in wild-type mice, but not in mice lacking ASMase. The extent of brain tissue damage was decreased and behavioral outcome improved in mice lacking ASMase. Neurons lacking ASMase exhibited decreased vulnerability to excitotoxicity and hypoxia, which was associated with decreased levels of intracellular calcium and oxyradicals. **Treatment** of mice with a drug that inhibits ASMase activity and ceramide production reduced ischemic neuronal injury and improved behavioral outcome, suggesting that drugs that inhibit this signaling pathway may prove beneficial in stroke patients.
CC 14-10 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 15
ST acidic **sphingomyelinase** brain ischemia ceramide cytokine neuron apoptosis
IT Nerve, disease
(death; pivotal role for acidic **sphingomyelinase** in cerebral ischemia-**induced** ceramide and cytokine production and neuronal apoptosis)
IT mRNA
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(inflammatory cytokine; pivotal role for acidic **sphingomyelinase** in cerebral ischemia-**induced** ceramide and cytokine production and neuronal apoptosis)
IT Cytokines
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inflammatory, mRNA; pivotal role for acidic **sphingomyelinase** in cerebral ischemia-**induced** ceramide and cytokine production and neuronal apoptosis)
IT **Brain, disease**
(ischemia, focal; pivotal role for acidic **sphingomyelinase** in cerebral ischemia-**induced ceramide** and cytokine production and neuronal apoptosis)
IT **Brain, disease**
(ischemia; pivotal role for acidic **sphingomyelinase** in

cerebral ischemia-**induced ceramide** and cytokine production and neuronal apoptosis)

IT Interleukin 1α
Interleukin 1β
Interleukin 2
Tumor necrosis factors
RL: BSU (Biological study, unclassified); BIOL (Biological study) (mRNA; pivotal role for acidic **sphingomyelinase** in cerebral ischemia-**induced** ceramide and cytokine production and neuronal apoptosis)

IT Cell death
(neuron; pivotal role for acidic **sphingomyelinase** in cerebral ischemia-**induced** ceramide and cytokine production and neuronal apoptosis)

IT Brain
Hypoxia, animal
Second messenger system
(pivotal role for acidic **sphingomyelinase** in cerebral ischemia-**induced** ceramide and cytokine production and neuronal apoptosis)

IT Reactive oxygen species
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(pivotal role for acidic **sphingomyelinase** in cerebral ischemia-**induced** ceramide and cytokine production and neuronal apoptosis)

IT **Ceramides**
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(pivotal role for acidic **sphingomyelinase** in **cerebral ischemia-induced** ceramide and cytokine production and neuronal apoptosis)

IT **Brain, disease**
(**stroke**; pivotal role for acidic **sphingomyelinase** in cerebral ischemia-**induced ceramide** and cytokine production and neuronal apoptosis)

IT 143011-72-7, G-CSF
RL: BSU (Biological study, unclassified); BIOL (Biological study) (mRNA; pivotal role for acidic **sphingomyelinase** in cerebral ischemia-**induced** ceramide and cytokine production and neuronal apoptosis)

IT 7440-70-2, Calcium, biological studies 7782-44-7D, Oxygen, radicals, biological studies **9031-54-3**, Acidic **sphingomyelinase** 102784-33-8, Phosphatidylcholine-specific phospholipase C
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(pivotal role for acidic **sphingomyelinase** in cerebral ischemia-**induced** ceramide and cytokine production and neuronal apoptosis)

IT **9031-54-3**, Acidic **sphingomyelinase**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(pivotal role for acidic **sphingomyelinase** in cerebral ischemia-**induced** ceramide and cytokine production and neuronal apoptosis)

RN 9031-54-3 HCAPLUS
CN Sphingomyelinase C (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS

L161 ANSWER 4 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 9
ACCESSION NUMBER: 1998:370106 HCAPLUS
DOCUMENT NUMBER: 129:107396
TITLE: Effects of tumor necrosis factor-α on the coronary circulation of the rat isolated perfused heart: a potential role for thromboxane A2 and **sphingosine**
AUTHOR(S): Edmunds, N. J.; Woodward, B.
CORPORATE SOURCE: Department of Pharmacology, University of Bath, Bath, BA2 7AY, UK
SOURCE: British Journal of Pharmacology (**1998**), 124(3), 493-498
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 17 Jun 1998
AB The actions of tumor necrosis factor-α (TNF-α) on the coronary circulation were investigated in the rat isolated heart, perfused under constant flow, recirculating conditions. An early increase in coronary perfusion pressure (CPP) was observed upon **treatment** with TNF-α (increase in CPP 10 min after TNF-α **treatment**: 45 mmHg vs. control: 15 mmHg). The role of **sphingosine**, prostanoids and endothelins, in this coronary constrictor action, was investigated with the use of **pharmacol.** inhibitors and antagonists. The TNF-α induced increase in coronary tone was blocked by indomethacin, 10 μM (increase in CPP after 10 min: 13 mmHg vs. TNF-α alone). The thromboxane receptor antagonist GR32191, 10 μM, attenuated the TNF-α induced coronary constriction (12 mmHg vs. TNF-α alone), as did the joint thromboxane A2 synthesis inhibitor and receptor antagonist ZD1542, 10 μM (8 ± mmHg vs. TNF-α alone). The ceramidase inhibitor N-oleoylethanolamine (NOE), 1 μM, also blocked the TNF-α induced response (8 mmHg vs. TNF-α alone). In contrast, the coronary constrictor action of TNF-α was not inhibited by the endothelinA/B receptor antagonist bosentan, 3 μM (38 mmHg vs. TNF-α, P=NS). These data indicated that the early coronary vasoconstriction **induced** by TNF-α was **mediated** by both thromboxane A2 and **sphingosine**, suggesting an interaction between both the **sphingomyelinase** and phospholipase A2 metabolic pathways.
CC 14-3 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 2, 15
ST coronary circulation tumor necrosis factor thromboxane; **sphingosine** coronary circulation tumor necrosis factor; endotoxic shock coronary circulation TNF thromboxane
IT Circulation
(coronary; effects of tumor necrosis factor-α on coronary circulation of rat isolated perfused heart and potential role for thromboxane A2 and **sphingosine** in relation to endotoxic shock)
IT Vasoconstriction
(effects of tumor necrosis factor-α on coronary circulation of rat isolated perfused heart and potential role for thromboxane A2 and **sphingosine** in relation to endotoxic shock)
IT Tumor necrosis factors
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(effects of tumor necrosis factor-α on coronary circulation of rat isolated perfused heart and potential role for thromboxane A2 and

sphingosine in relation to endotoxic shock)
IT **Sphingosines**
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**effects** of tumor necrosis factor-α on **coronary** circulation of rat isolated perfused **heart** and potential role for thromboxane A2 and **sphingosine** in relation to endotoxic shock)
IT Toxins
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(endotoxins, shock from; effects of tumor necrosis factor-α on coronary circulation of rat isolated perfused heart and potential role for thromboxane A2 and **sphingosine** in relation to endotoxic shock)
IT **Shock (circulatory collapse)**
(septic; effects of tumor necrosis factor-α on coronary circulation of rat isolated perfused heart and potential role for thromboxane A2 and **sphingosine** in relation to endotoxic shock)
IT Metabolic pathways
(**sphingomyelinase** and phospholipase A2; **effects** of tumor necrosis factor-α on coronary circulation of rat isolated perfused heart and potential role for thromboxane A2 and **sphingosine** in relation to endotoxic shock)
IT 57576-52-0, Thromboxane A2
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(effects of tumor necrosis factor-α on coronary circulation of rat isolated perfused heart and potential role for thromboxane A2 and **sphingosine** in relation to endotoxic shock)
IT 9001-84-7, Phospholipase A2 **9031-54-3**, **Sphingomyelinase** C
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(metabolic pathway; **effects** of tumor necrosis factor-α on coronary circulation of rat isolated perfused heart and potential role for thromboxane A2 and **sphingosine** in relation to endotoxic shock)
IT **9031-54-3**, **Sphingomyelinase** C
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(metabolic pathway; **effects** of tumor necrosis factor-α on coronary circulation of rat isolated perfused heart and potential role for thromboxane A2 and **sphingosine** in relation to endotoxic shock)
RN 9031-54-3 HCAPLUS
CN Sphingomyelinase C (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L161 ANSWER 5 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 14
ACCESSION NUMBER: 1994:570273 HCAPLUS
DOCUMENT NUMBER: 121:170273
TITLE: brain content of **glycosphingolipids** after

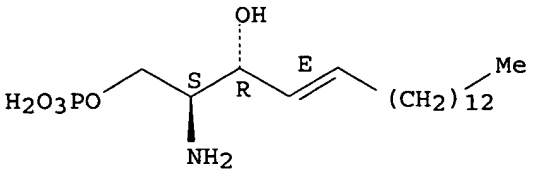
oral **administration** of monosialogangliosides GM1 and LIGA20 to rats
AUTHOR(S): Polo, A.; Kirschner, G.; Guidotti, A.; Costa, E.
CORPORATE SOURCE: Med. Sch., Georgetown Univ., Washington, DC, 20007, USA
SOURCE: Molecular and Chemical Neuropathology (**1994**), 21(1), 41-53
CODEN: MCHNEM; ISSN: 1044-7393
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 15 Oct 1994
AB Natural (GM1) and semisynthetic [113-Neu-5-AcGgOse4-2-D-erythro-1, 3-dihydroxy-2-dichloroacetylamide-4-trans-octadecene (LIGA20)] **glycosphingolipids**, given parenterally, protect neurons against glutamate-**induced** death without producing the side effects typical of glutamate receptor antagonists. Chronic glutamate-related neurotoxicity (e.g., in recurring strokes in elderly hypertensive patients, and in Parkinson disease) could be **prevented** also by **glycosphingolipids treatment**, but this **therapeutic** intervention will require a protracted **administration** of orally active **glycosphingolipids.** Here the authors demonstrate that 3-6 h after oral **administration** of 68 μmol/kg of LIGA20 and GM1 to rats, the brain content of LIGA20 is 50-fold higher than that of GM1. The brain concentration of LIGA20 remains elevated for at least 12-24 h. Because the LIGA20 that reaches the brain is **slowly** metabolized, repeated oral **administrations** of this **glycosphingolipid** can yield to its accumulation in brain, and can yield various brain levels depending on the dose and frequency of drug **administration.** In contrast this is not possible with GM1, which given orally for 7 d, cannot accumulate in brain in **pharmacol.** significant concns.
CC 1-11 (Pharmacology)
ST **glycosphingolipid** monosialoganglioside LIGA20 brain
IT **Brain, disease**
(**glycosphingolipid treatment** by, LIGA20 and ganglioside GM1 accumulation of, in brain and plasma)
IT **104443-62-1**, Ganglioside GM1
RL: BIOL (Biological study)
(LIGA20 comparison with, as orally active **glycosphingolipids**, **brain** levels in relation to)
IT 126586-85-4, LIGA 20
RL: BIOL (Biological study)
(brain content of **glycosphingolipids** after oral **administration** of)
IT **104443-62-1**, Ganglioside GM1
RL: BIOL (Biological study)
(LIGA20 comparison with, as orally active **glycosphingolipids**, **brain** levels in relation to)
RN 104443-62-1 HCAPLUS
CN Ceramide, 1-O-[O-β-D-galactopyranosyl-(1→3)-O-2-(acetylamino)-2-deoxy-β-D-galactopyranosyl-(1→4)-O-[N-acetyl-α-neuraminosyl-(2→3)]-O-β-D-galactopyranosyl-(1→4)-β-D-glucopyranosyl]- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L161 ANSWER 6 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:257262 HCAPLUS
DOCUMENT NUMBER: 140:336147
TITLE: Point-Counterpoint of **Sphingosine**

1-Phosphate Metabolism
AUTHOR(S): Saba, Julie D.; Hla, Timothy
CORPORATE SOURCE: Research Institute, Children's Hospital of Oakland, Oakland, CA, USA
SOURCE: Circulation Research (2004), 94(6), 724-734
CODEN: CIRUAL; ISSN: 0009-7330
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
ED Entered STN: 29 Mar 2004
AB A review. **Sphingosine** 1-phosphate (S1P), an evolutionarily conserved bioactive lipid **mediator**, is now recognized as a potent modulator of cell regulation. In vertebrates, S1P interacts with cell surface G protein-coupled receptors of the EDG family and induces profound effects in a variety of organ systems. Indeed, an S1P receptor agonist is undergoing clin. trials to combat immune-mediated transplant rejection. Recent information on S1P receptor biol. suggests potential utility in the control of cardiovascular processes, including angiogenesis, vascular permeability, arteriogenesis, and vasospasm. However, studies from diverse invertebrates, such as yeast, Dictyostelium, Drosophila, and Caenorhabditis elegans have shown that S1P is involved in important regulatory functions in the apparent absence of EDG S1P receptor homologs. Metabolic pathways of S1P synthesis, degradation, and release have recently been described at the mol. level. Genetic and biochem. studies of these enzymes have illuminated the importance of S1P signaling systems both inside and outside of cells. The revelation of receptor-dependent pathways, as well as novel metabolic/intracellular pathways has provided new biol. insights and may ultimately pave the way for the development of novel **therapeutic** approaches for cardiovascular diseases.
CC 13-0 (Mammalian Biochemistry)
Section cross-reference(s): 12, 14
ST review **sphingosine** phosphate receptor function metab cardiovascular system disease
IT Signal transduction, biological
(involving S1P; **sphingosine** 1-phosphate (S1P) function and metabolism in cardiovascular system)
IT Cardiovascular system
Cardiovascular system, disease
Human
(**sphingosine** 1-phosphate (S1P) function and metabolism in cardiovascular system)
IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**sphingosine** 1-phosphate; **sphingosine** 1-phosphate (S1P) function and metabolism in cardiovascular system)
IT **26993-30-6**, **Sphingosine** 1-phosphate
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**sphingosine** 1-phosphate (S1P) function and metabolism in **cardiovascular** system)
IT **26993-30-6**, **Sphingosine** 1-phosphate
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**sphingosine** 1-phosphate (S1P) function and metabolism in **cardiovascular** system)
RN 26993-30-6 HCAPLUS
CN 4-Octadecene-1,3-diol, 2-amino-, 1-(dihydrogen phosphate), (2S,3R,4E)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



REFERENCE COUNT: 113 THERE ARE 113 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L161 ANSWER 7 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:184585 HCAPLUS
DOCUMENT NUMBER: 137:138098
TITLE: Lysophospholipid growth factors and their G protein-coupled receptors in immunity, coronary artery disease, and cancer
AUTHOR(S): Goetzl, Edward J.; Graeler, Markus; Huang, Mei-Chuan; Shankar, Geetha
CORPORATE SOURCE: Departments of Medicine and Microbiology, University of California, San Francisco, CA, 94143-0711, USA
SOURCE: TheScientificWorld [online computer file] (2002), 2, 324-338
CODEN: THESAS; ISSN: 1532-2246
URL: http://216.25.253.202/TSWJaudit/pdf/2002.03.124.pdf
PUBLISHER: TheScientificWorld, Inc.
DOCUMENT TYPE: Journal; **General Review**; (online computer file)
LANGUAGE: English
ED Entered STN: 15 Mar 2002
AB A review. The physiol. lysophospholipids (LPLs), exemplified by lysophosphatidic acid (LPA) and **sphingosine** 1-phosphate (S1P), are omnific **mediators** of normal cellular proliferation, survival, and functions. Although both LPA and S1P attain micromolar concns. in many biol. fluids, numerous aspects of their biosynthesis, transport, and metabolic degradation are unknown. Eight members of a new subfamily of G protein-coupled LPA/S1P receptors, originally termed Edg Rs, bind either LPA or S1P with high affinity and transduce a series of growth-related and/or cytoskeleton-based functional responses. The most critical areas of LPL biol. and pathobiol. are neural development and neurodegeneration, immunity, atherosclerosis and myocardial injury, and cancer. Data from analyzes of T cells established two basic points: (1) the plasticity and adaptability of expression of LPA/S1P Rs by some cells as a function of activation, and (2) the role of opposing signals from two different receptors for the same ligand as a mechanism for fine control of effects of LPLs. In the heart, LPLs may promote coronary atherosclerosis, but are effectively cytoprotective for hypoxic cardiac myocytes and those exposed to oxygen free radicals. The findings of production of LPA by some types of tumor cells, overexpression of selected sets of LPA receptors by the same tumor cells, and augmentation of the effects of protein growth factors by LPA have suggested pathogenetic roles for the LPLs in cancer. The breadth of physiol. and pathol. activities of LPLs emphasizes the importance of developing bioavailable nonlipid agonists and antagonists of the LPA/S1P receptors for diverse **therapeutic** applications.
CC 14-0 (Mammalian Pathological Biochemistry)
ST review lysophospholipid **sphingosine** receptor heart disease neurodegeneration cancer
IT Human

Immunity
Neoplasm
(**altered** metabolism of lysophospholipid and **sphingosine** via G protein-coupled receptors in heart, neurodegenerative diseases, and cancer)

IT G protein-coupled receptors
Lysophospholipids
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(**altered** metabolism of lysophospholipid and **sphingosine** via G protein-coupled receptors in heart, neurodegenerative diseases, and cancer)

IT **Artery, disease**
(coronary; **altered** metabolism of lysophospholipid and **sphingosine** via G protein-coupled receptors in heart, neurodegenerative diseases, and cancer)

IT Nerve, disease
(degeneration; **altered** metabolism of lysophospholipid and **sphingosine** via G protein-coupled receptors in heart, neurodegenerative diseases, and cancer)

IT Receptors
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(lysophosphatidic acid; **altered** metabolism of lysophospholipid and **sphingosine** via G protein-coupled receptors in heart, neurodegenerative diseases, and cancer)

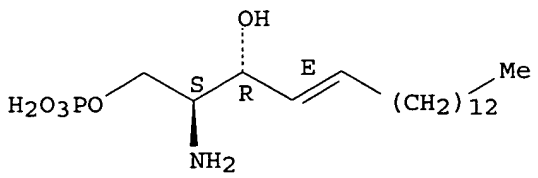
IT Receptors
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(**sphingosine** 1-phosphate; **altered** metabolism of lysophospholipid and **sphingosine** via G protein-coupled receptors in heart, neurodegenerative diseases, and cancer)

IT **26993-30-6**, **Sphingosine** 1-phosphate
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(**altered** metabolism of lysophospholipid and **sphingosine** via G protein-coupled receptors in **heart**, neurodegenerative diseases, and cancer)

IT **26993-30-6**, **Sphingosine** 1-phosphate
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(**altered** metabolism of lysophospholipid and **sphingosine** via G protein-coupled receptors in **heart**, neurodegenerative diseases, and cancer)

RN 26993-30-6 HCAPLUS
CN 4-Octadecene-1,3-diol, 2-amino-, 1-(dihydrogen phosphate), (2S,3R,4E)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L161 ANSWER 8 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:396835 HCAPLUS
DOCUMENT NUMBER: 135:19492
TITLE: Preparation of **sphingosine** derivatives as **preventive** or **therapeutic** remedies for cerebrovascular disorders
INVENTOR(S): Kobori, Takeo; Sugimoto, Kikuo; Goda, Kenichi; Taguchi, Minoru
PATENT ASSIGNEE(S): Taisho Pharmaceutical Co.,ltd., Japan; Sagami Chemical Research Center
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001038295	A1	20010531	WO 2000-JP8229	20001122 <--
W: AU, CA, CN, KR, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
JP 2001213858	A2	20010807	JP 2000-355117	20001122 <--
PRIORITY APPLN. INFO.:			JP 1999-332165 A	19991124 <--

OTHER SOURCE(S): MARPAT 135:19492
ED Entered STN: 01 Jun 2001
AB Title compds. [CnH2n+1CH:CHCHOHCH(NHR1)CH2YC(:W)ZR2; R1 = H, (CH3)3CCO, (CH3)2CHCO, BOC, COCH2NHBOC, COCH2NH2, COCOOEt, COCOOH; R2 = H, OH, CH2CH2N(CH3)2, CH2COOH, 4-HOOCC6H4, heterocycle; W = O, S; Y = O, NH; Z = NH, NCH3, NOH; n = an integer of 1 to 20] and **pharmaceutically** acceptable salts are prepared and biol. tested. Title derivs. and salts are useful as **preventive** or **therapeutic** drugs for cerebrovascular disorders such as cerebral hemorrhage and cerebral infarction; head injuries; senile dementia; degenerative diseases of cranial nerve such as Alzheimer disease and Parkinson disease; diabetes; obesity; arteriosclerosis; inflammatory diseases; immunol. diseases; cancers; kidney diseases; and heart diseases.
IC ICM C07C271-08
ICS C07C271-12; C07C271-16; C07C271-20; C07C271-22; C07C271-28; C07C275-20; C07C275-42; C07C311-53; C07C323-43; C07D213-53; C07D213-75; C07D231-56; C07D233-61; C07D233-64; C07D241-20; C07D257-06; C07D277-46; C07D285-12; C07D295-12
CC 26-3 (Biomolecules and Their Synthetic Analogs)
Section cross-reference(s): 1, 63
ST **sphingosine** prepn **prevention therapy** remedy cerebrovascular disorders
IT Immunity
(disorder; preparation of **sphingosine** derivs. as remedies)
IT **Brain, disease**
(hemorrhage; preparation of **sphingosine** derivs. as **preventive** or **therapeutic** remedies for cerebrovascular disorders)
IT **Brain, disease**
(infarction; preparation of **sphingosine** derivs. as **preventive** or **therapeutic** remedies for cerebrovascular disorders)
IT Head

(injury; preparation of **sphingosine** derivs. as **preventive** or **therapeutic** remedies for cerebrovascular disorders)

IT Diabetes mellitus
(preparation of **sphingosine** derivs. as **preventive** or **therapeutic** remedies)

IT **Alzheimer's disease**
Diabetes insipidus
Parkinson's disease
(preparation of **sphingosine** derivs. as **preventive** or **therapeutic** remedies for cerebrovascular disorders)

IT **Arteriosclerosis**
Heart, disease
Kidney, disease
(preparation of **sphingosine** derivs. as remedies)

IT Mental disorder
(senile psychosis; preparation of **sphingosine** derivs. as **preventive** or **therapeutic** remedies for cerebrovascular disorders)

IT Anti-inflammatory agents
Antidiabetic agents
Antiobesity agents
Antitumor agents
(**sphingosines**)

IT 342649-74-5P 342649-76-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of **sphingosine** derivs. as **preventive** or **therapeutic** remedies for cerebrovascular disorders)

IT 342629-39-4P 342629-49-6P 342649-77-8P 342649-80-3P 342649-81-4P
342649-82-5P 342649-83-6P 342649-85-8P 342649-86-9P 342649-87-0P
342649-88-1P 342649-89-2P 342649-90-5P 342649-91-6P 342649-93-8P
342649-94-9P 342649-95-0P 342649-96-1P 342649-97-2P 342649-98-3P
342649-99-4P 342650-00-4P 342650-01-5P 342650-02-6P 342650-03-7P
342650-04-8P 342650-06-0P 342650-08-2P 342650-11-7P 342650-15-1P
342650-16-2P 342650-28-6P 342650-30-0P 342650-32-2P 342650-38-8P
342650-39-9P 342650-40-2P 342650-42-4P 342650-43-5P 342650-44-6P
342650-45-7P 342650-46-8P 342650-48-0P 342650-49-1P 342650-50-4P
342650-52-6P 342650-53-7P 342650-54-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of **sphingosine** derivs. as **preventive** or **therapeutic** remedies for cerebrovascular disorders)

IT 104-96-1, 4-(Methylthio)aniline 3731-53-1, 4-Pyridinylmethylamine
18162-48-6, tert-Butyldimethylsilyl chloride 71026-66-9,
4-(tert-Butoxycarbonylamino)aniline 116467-63-1 342655-75-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of **sphingosine** derivs. as **preventive** or **therapeutic** remedies for cerebrovascular disorders)

IT **123-78-4P** 342649-66-5P 342649-68-7P 342649-69-8P
342649-70-1P 342649-71-2P 342649-72-3P 342649-73-4P 342655-60-1P
342655-61-2P 342655-62-3P 342655-63-4P 342655-64-5P 342655-65-6P
342655-66-7P 342655-67-8P 342655-68-9P 342655-69-0P 342655-70-3P
342655-71-4P 342655-72-5P 342655-73-6P 342655-74-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of **sphingosine** derivs. as **preventive** or **therapeutic** remedies for **cerebrovascular** disorders)

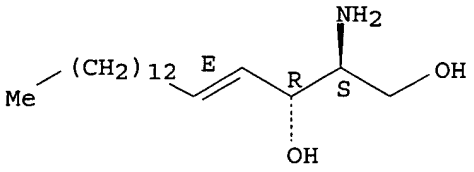
IT 342650-36-6P 342650-56-0P 342650-64-0P
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of **sphingosine** derivs. as **preventive** or **therapeutic** remedies for cerebrovascular disorders)

IT 342629-33-8P 342629-35-0P 342629-37-2P 342629-41-8P 342629-43-0P
342629-45-2P 342631-84-9P 342649-75-6P 342649-78-9P 342649-79-0P
342649-84-7P 342649-92-7P 342650-05-9P 342650-07-1P 342650-09-3P
342650-10-6P 342650-12-8P 342650-13-9P 342650-14-0P 342650-17-3P
342650-18-4P 342650-19-5P 342650-20-8P 342650-21-9P 342650-22-0P
342650-23-1P 342650-24-2P 342650-25-3P 342650-26-4P 342650-27-5P
342650-29-7P 342650-31-1P 342650-33-3P 342650-34-4P 342650-35-5P
342650-37-7P 342650-41-3P 342650-47-9P 342650-51-5P 342650-55-9P
342650-57-1P 342650-58-2P 342650-59-3P 342650-60-6P 342650-61-7P
342650-62-8P 342650-63-9P 342650-65-1P 342655-76-9P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of **sphingosine** derivs. as **preventive** or **therapeutic** remedies for cerebrovascular disorders)

IT **123-78-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of **sphingosine** derivs. as **preventive** or **therapeutic** remedies for **cerebrovascular** disorders)

RN 123-78-4 HCAPLUS
CN 4-Octadecene-1,3-diol, 2-amino-, (2S,3R,4E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L161 ANSWER 9 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:137382 HCAPLUS
DOCUMENT NUMBER: 134:190008
TITLE: Neutral **sphingomyelinases** of mammalian brain and cloning and expression of cDNAs encoding them
INVENTOR(S): Hofmann, Kay
PATENT ASSIGNEE(S): Memorec Stoffel G.m.b.H. Medizinisch-Molekulare Entwicklung, Germany
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012818	A1	20010222	WO 2000-EP7889	20000812 <--

W: JP, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

DE 19938671	A1	20010222	DE 1999-19938671	19990814 <--
EP 1204757	A1	20020515	EP 2000-956442	20000812 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
JP 2003507015	T2	20030225	JP 2001-516905	20000812 <--
PRIORITY APPLN. INFO.:			DE 1999-19938671 A	19990814 <--
			EP 2000-100873 A	20000118 <--
			WO 2000-EP7889 W	20000812 <--

OTHER SOURCE(S): MARPAT 134:190008
ED Entered STN: 25 Feb 2001
AB Neutral **sphingomyelinases** of mammalian brain that have the following sequence motifs: X1-X2-X3-X4-D-Y-X5 and X6-X7-T-D-H-X8, (X1, X6 = A, G; X2, X3 = R, K; X4, X5, X7, X8 = I, L, V, M) and cDNAs encoding them are isolated and characterized. The enzymes and the cDNAs may be of use in the diagnosis and **treatment** of disease (no data).
IC ICM C12N015-55
ICS C12N009-16; C12N005-10; C07K016-40; G01N033-50; A61K038-43; A01K067-027
CC 7-2 (Enzymes)
ST brain neutral **sphingomyelinase** cDNA mouse human cloning expression sequence
IT Animal cell line
(Hek 293, expression host; neutral **sphingomyelinases** of mammalian brain and cloning and expression of cDNAs encoding them)
IT Animal cell line
(JURKAT, expression host; neutral **sphingomyelinases** of mammalian brain and cloning and expression of cDNAs encoding them)
IT Animal cell line
(U937, expression host; neutral **sphingomyelinases** of mammalian brain and cloning and expression of cDNAs encoding them)
IT **Ceramides**
RL: BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(as product of neutral **sphingomyelinase** hydrolysis of **sphingomyelin**; neutral **sphingomyelinases** of mammalian **brain** and cloning and expression of cDNAs encoding them)
IT **Sphingomyelins**
RL: BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(as substrate for neutral **sphingomyelinase**; neutral **sphingomyelinases** of mammalian **brain** and cloning and expression of cDNAs encoding them)
IT Apoptosis
Cell differentiation
Cell proliferation
(brain neutral **sphingomyelinase** in diagnosis and **treatment** of disease of; neutral **sphingomyelinases** of mammalian brain and cloning and expression of cDNAs encoding them)
IT **Arteriosclerosis**
Inflammation
Neoplasm
(brain neutral **sphingomyelinase** in diagnosis and **treatment** of; neutral **sphingomyelinases** of mammalian brain and cloning and expression of cDNAs encoding them)
IT Gene **therapy**
(cDNA for brain neutral **sphingomyelinase** in; neutral **sphingomyelinases** of mammalian brain and cloning and expression

of cDNAs encoding them)
IT Gene, animal
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(cDNA, for neutral **sphingomyelinase**; neutral **sphingomyelinases** of mammalian brain and cloning and expression of cDNAs encoding them)
IT Metabolism, animal
(disorder, brain neutral **sphingomyelinase** in diagnosis and **treatment** of; neutral **sphingomyelinases** of mammalian brain and cloning and expression of cDNAs encoding them)
IT cDNA sequences
(for brain neutral **sphingomyelinase** of human and mouse; neutral **sphingomyelinases** of mammalian brain and cloning and expression of cDNAs encoding them)
IT Drug screening
(for effectors of brain neutral **sphingomyelinase**; neutral **sphingomyelinases** of mammalian brain and cloning and expression of cDNAs encoding them)
IT Diagnosis
(mol., brain neutral **sphingomyelinase** as marker in; neutral **sphingomyelinases** of mammalian brain and cloning and expression of cDNAs encoding them)
IT Brain
(neutral **sphingomyelinases** of mammalian brain and cloning and expression of cDNAs encoding them)
IT Protein sequences
(of brain neutral **sphingomyelinase** of human and mouse; neutral **sphingomyelinases** of mammalian brain and cloning and expression of cDNAs encoding them)
IT Protein motifs
(of brain neutral **sphingomyelinases**; neutral **sphingomyelinases** of mammalian brain and cloning and expression of cDNAs encoding them)
IT Molecular cloning
(of cDNA for brain neutral **sphingomyelinase**; neutral **sphingomyelinases** of mammalian brain and cloning and expression of cDNAs encoding them)
IT Mouse (Mus musculus)
(**sphingomyelinases** of human and; neutral **sphingomyelinases** of mammalian brain and cloning and expression of cDNAs encoding them)
IT Antibodies
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(to brain neutral **sphingomyelinase**; neutral **sphingomyelinases** of mammalian brain and cloning and expression of cDNAs encoding them)
IT Mammal (Mammalia)
Rodent
(transgenic, with **alter** levels of brain neutral **sphingomyelinase**; neutral **sphingomyelinases** of mammalian brain and cloning and expression of cDNAs encoding them)
IT 288287-50-3 288287-51-4
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(amino acid sequence; neutral **sphingomyelinases** of mammalian brain and cloning and expression of cDNAs encoding them)
IT 107-73-3, Phosphocholine

RL: BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(as product of neutral **sphingomyelinase** hydrolysis of **sphingomyelin**; neutral **sphingomyelinases** of mammalian brain and cloning and expression of cDNAs encoding them)

IT 57-88-5, Cholesterol, biological studies
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(brain neutral **sphingomyelinase** in **treatment** of disorders of metabolism of; neutral **sphingomyelinases** of mammalian brain and cloning and expression of cDNAs encoding them)

IT **9031-54-3**, **Sphingomyelinase**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(neutral **sphingomyelinases** of mammalian brain and cloning and expression of cDNAs encoding them)

IT 269042-89-9 269042-95-7
RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nucleotide sequence; neutral **sphingomyelinases** of mammalian brain and cloning and expression of cDNAs encoding them)

IT 327040-94-8 327040-99-3
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(peptide motif of brain neutral **sphingomyelinases**; neutral **sphingomyelinases** of mammalian brain and cloning and expression of cDNAs encoding them)

IT **9031-54-3**, **Sphingomyelinase**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(neutral **sphingomyelinases** of mammalian brain and cloning and expression of cDNAs encoding them)

RN 9031-54-3 HCAPLUS
CN Sphingomyelinase C (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L161 ANSWER 10 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:872383 HCAPLUS
DOCUMENT NUMBER: 142:51330
TITLE: **Sphingomyelinase** separated from bovine brain and purification method thereof
INVENTOR(S): Jung, Gwang Muk; Jung, Seong Yun; Kim, Dae Kyong
PATENT ASSIGNEE(S): SK Corporation, S. Korea
SOURCE: Repub. Korean Kongkae Taeho Kongbo, No pp. given
CODEN: KRXXA7
DOCUMENT TYPE: Patent
LANGUAGE: Korean
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
KR 2001045120	A	20010605	KR 1999-48275	19991103 <--
PRIORITY APPLN. INFO.:			KR 1999-48275	19991103 <--

ED Entered STN: 21 Oct 2004
AB Provided are **sphingomyelinase** separated from bovine brain and a method for purifying the enzyme so as to be used in developing **medications** against brain diseases such as Parkinson's disease and Alzheimer disease. **Sphingomyelinase**, integral membrane protein, exists in nerve cell membranes of bovine brain and hydrolyzes **sphingomyelin** to produce ceramide and phosphocholine. The enzyme is active at pH 6.0-9.0, in particular, pH 7.5, depending on Mg2+. A method for purifying **sphingomyelinase** is comprised of the next steps of: homogenizing tissues of bovine brain and eliminating cell remnants and nucleus; obtaining exts. from centrifuged cell membrane pellets in buffer solution containing ammonium sulfate; destroying the exts. in buffer solution having X-100 which passed through anion exchange chromatog.; and purifying supernatant obtained after centrifugation through a series of chromatogs.
IC ICM C07K001-14
CC 7-1 (Enzymes)
Section cross-reference(s): 13
ST Bos brain disease **sphingomyelinase** purifn **sphingomyelin**
IT **Alzheimer's disease**
Bos taurus
Brain
Parkinson's disease
Purification
(**sphingomyelinase** separated from bovine brain and purification method thereof)
IT **Sphingomyelins**
RL: BCP (Biochemical process); BIOL (Biological study); PROC (Process)
(**sphingomyelinase** separated from bovine **brain** and purification method thereof)
IT **Ceramides**
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(**sphingomyelinase** separated from bovine **brain** and purification method thereof)
IT 107-73-3P, Phosphocholine
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(**sphingomyelinase** separated from bovine brain and purification method thereof)
IT **9031-54-3P, Sphingomyelinase**
RL: BSU (Biological study, unclassified); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation)
(**sphingomyelinase** separated from bovine brain and purification method thereof)
IT **9031-54-3P, Sphingomyelinase**
RL: BSU (Biological study, unclassified); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation)
(**sphingomyelinase** separated from bovine brain and purification method thereof)
RN 9031-54-3 HCAPLUS
CN Sphingomyelinase C (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L161 ANSWER 11 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:705065 HCAPLUS
DOCUMENT NUMBER: 137:289041
TITLE: Angiogenesis **promoter** containing **sphingosine** 1-phosphate as active ingredient

INVENTOR(S): Kim, Gyu Won; Kim, Yeong Mi; Kwon, Young Guen; Lee, Ok Hui; Lee, Yu Mi; Mun, Eun Jeong
PATENT ASSIGNEE(S): S. Korea
SOURCE: Repub. Korean Kongkae Taeho Kongbo, No pp. given
CODEN: KRXXA7
DOCUMENT TYPE: Patent
LANGUAGE: Korean
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
KR 2001008569	A	20010205	KR 1999-26477	19990702 <--

PRIORITY APPLN. INFO.: KR 1999-26477 19990702 <--

ED Entered STN: 17 Sep 2002

AB An angiogenesis **promoter** containing **sphingosine** 1-phosphate as active ingredient is provided, which **promotes** an angiogenesis by binding with a cell receptor that exists in a vascular endothelial cell in vivo and in vitro. In vascular endothelial cell, EDG-1 is expressed more prevalently than EDG-3 and EDG-5, that means the vascular endothelial cell responds to **sphingosine** 1-phosphate. As the concentration of S1P increases, the mobility of the vascular endothelial cell increases as well. When **treating** the vascular endothelial cell with **sphingosine**, C2-ceramide, and lysophosphatidic acid, the mobility of vascular endothelial cell does not show change. An angiogenesis **promoter** is characterized by comprising **sphingosine** 1-phosphate as active ingredient and **pharmaceutically** acceptable carrier and by being used as **therapeutic** agents for burn, rheumatoid arthritis, ulcer, arteriosclerosis, myocardial infarction and the like.

IC ICM A61K031-66

CC 1-12 (Pharmacology)
Section cross-reference(s): 63

ST angiogenesis **promoter** **sphingosine** phosphate

IT **Arteriosclerosis**
Burn
Rheumatoid arthritis
Ulcer
(angiogenesis **promoter** containing **sphingosine** 1-phosphate as active ingredient)

IT Growth factors, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(endothelium-derived growth factors; angiogenesis **promoter** containing **sphingosine** 1-phosphate as active ingredient)

IT **Heart, disease**
(infarction; angiogenesis **promoter** containing **sphingosine** 1-phosphate as active ingredient)

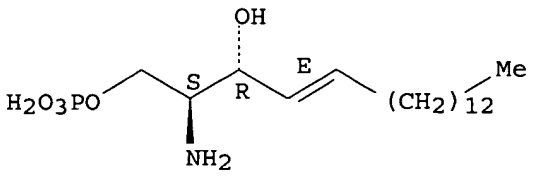
IT **Angiogenesis**
(**promoters**; angiogenesis **promoter** containing **sphingosine** 1-phosphate as active ingredient)

IT **26993-30-6, Sphingosine** 1-phosphate
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**angiogenesis promoter** containing **sphingosine** 1-phosphate as active ingredient)

IT **26993-30-6, Sphingosine** 1-phosphate
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**angiogenesis promoter** containing **sphingosine** 1-phosphate as active ingredient)

RN 26993-30-6 HCAPLUS
CN 4-Octadecene-1,3-diol, 2-amino-, 1-(dihydrogen phosphate), (2S,3R,4E)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L161 ANSWER 12 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:557590 HCAPLUS
DOCUMENT NUMBER: 133:279104
TITLE: **Sphingosine** 1-phosphate signalling in mammalian cells
AUTHOR(S): Pyne, Susan; Pyne, Nigel J.
CORPORATE SOURCE: Department of Physiology and Pharmacology, Strathclyde Institute for Biomedical Sciences, University of Strathclyde, Glasgow, G4 0NR, UK
SOURCE: Biochemical Journal (**2000**), 349(2), 385-402
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
ED Entered STN: 14 Aug 2000
AB A review with 174 refs. **Sphingosine** 1-phosphate is formed in cells in response to diverse stimuli, including growth factors, cytokines, G-protein-coupled receptor agonists, antigen, etc. Its production is catalyzed by **sphingosine** kinase, while degradation is either via cleavage to produce palmitaldehyde and phosphoethanolamine or by dephosphorylation. In this review we discuss the most recent advances in our understanding of the role of the enzymes involved in metabolism of this lysolipid. **Sphingosine** 1-phosphate can also bind to members of the endothelial differentiation gene (EDG) G-protein-coupled receptor family [namely EDG1, EDG3, EDG5 (also known as H218 or AGR16), EDG6 and EDG8] to elicit biol. responses. These receptors are coupled differentially via Gi, Gq, G12/13 and Rho to multiple effector systems, including adenylate cyclase, phospholipases C and D, extracellular-signal-regulated kinase, c-Jun N-terminal kinase, p38 mitogen-activated protein kinase and non-receptor tyrosine kinases. These signaling pathways are linked to transcription factor activation, cytoskeletal proteins, adhesion mol. expression, caspase activities, etc. Therefore **sphingosine** 1-phosphate can affect diverse biol. responses, including mitogenesis, differentiation, migration and apoptosis, via receptor-dependent mechanisms. Addnl., **sphingosine** 1-phosphate has been proposed to play an intracellular role, for example in Ca2+ mobilization, activation of non-receptor tyrosine kinases, inhibition of caspases, etc. We review the evidence for both intracellular and extracellular actions, and extensively discuss future approaches that will ultimately resolve the question of dual action. Certainly, **sphingosine** 1-phosphate will prove to be unique if it **elicits** both extra- and intra-cellular actions. Finally, we review the evidence that implicates **sphingosine** 1-phosphate in pathophysiol. disease states, such as cancer, angiogenesis and inflammation. Thus there is a need for the

development of new **therapeutic** compds., such as receptor antagonists. However, identification of the most suitable targets for drug intervention requires a full understanding of the signaling and action profile of this **lysosphingolipid.** This article describes where the research field is in relation to achieving this aim.

CC 13-0 (Mammalian Biochemistry)
Section cross-reference(s): 14

ST review **sphingosine** phosphate signaling mammalian cell

IT Animal cell
(mammalian; **sphingosine** 1-phosphate signaling in mammalian cells)

IT **Sphingolipids**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabolism; **sphingosine** 1-phosphate signaling in mammalian cells)

IT **Angiogenesis**
Inflammation
Neoplasm
(**sphingosine** 1-phosphate role in pathophysiol. disease states)

IT Signal transduction, biological
(**sphingosine** 1-phosphate signaling in mammalian cells)

IT G protein-coupled receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**sphingosine** 1-phosphate signaling in mammalian cells)

IT **Enzymes, biological studies**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**sphingosine** 1-phosphate-forming and -metabolizing; **sphingosine** 1-phosphate signaling in mammalian cells)

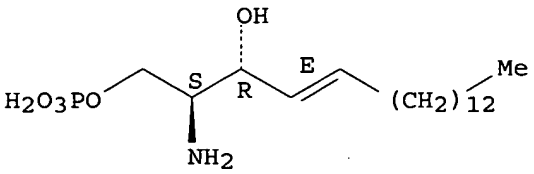
IT **26993-30-6, Sphingosine** 1-phosphate
RL: ANT (Analyte); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(**sphingosine** 1-phosphate signaling in mammalian cells)

IT **26993-30-6, Sphingosine** 1-phosphate
RL: ANT (Analyte); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(**sphingosine** 1-phosphate signaling in mammalian cells)

RN 26993-30-6 HCAPLUS

CN 4-Octadecene-1,3-diol, 2-amino-, 1-(dihydrogen phosphate), (2S,3R,4E)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



REFERENCE COUNT: 174 THERE ARE 174 CITED REFERENCES AVAILABLE FOR

THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L161 ANSWER 13 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:124743 HCAPLUS
DOCUMENT NUMBER: 132:263434
TITLE: Rapid activation of neutral **sphingomyelinase** by hypoxia-reoxygenation of cardiac myocytes
AUTHOR(S): Hernandez, Olga M.; Discher, Daryl J.; Bishopric, Nanette H.; Webster, Keith A.
CORPORATE SOURCE: Department of Molecular and Cellular Pharmacology, University of Miami Medical Center, Miami, FL, 33136, USA
SOURCE: Circulation Research (**2000**), 86(2), 198-204
CODEN: CIRUAL; ISSN: 0009-7330
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 24 Feb 2000
AB Elevated levels of oxygen free radicals have been implicated in the pathways of reperfusion injury to myocardial tissue. The targets for free radicals may include specific as well as random intracellular components, and part of the cellular response is the induction of extracellularly activated and stress-activated kinases. The intermediate signals that initiate these stress responses are not known. Here the authors show that one of the earliest responses of cardiac myocytes to hypoxia and reoxygenation is the activation of neutral **sphingomyelinase** and accumulation of ceramide. Ceramide increased abruptly after reoxygenation, peaking at 10 min with 225% of the control level. Neutral **sphingomyelinase** activity was **induced** with similar kinetics, and both activities remained elevated for several hours. C-Jun N-terminal kinase (JNK) was also activated within the same time frame. **Treatment** of cardiac myocytes with extracellular ceramides also activated JNK. Pretreating cells with antioxidants quenched **sphingomyelinase** activation, ceramide accumulation, and JNK activation. Ceramide did not accumulate in reoxygenated nonmuscle fibroblasts, and JNK was not activated by reoxygenation in these cells. The results identify neutral **sphingomyelinase** activation as one of the earliest responses of cardiac myocytes to the redox stress imposed by hypoxia-reoxygenation. The results are consistent with a pathway of ceramide-mediated activation of JNK.
CC 14-5 (Mammalian Pathological Biochemistry)
ST neutral **sphingomyelinase** hypoxia reoxygenation cardiac myocyte
IT **Ceramides**
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(accumulation; rapid activation of neutral **sphingomyelinase** by hypoxia-reoxygenation of **cardiac** myocytes in relation to)
IT **Reperfusion**
(injury; rapid activation of neutral **sphingomyelinase** by hypoxia-reoxygenation of cardiac myocytes in relation to)
IT Heart
(myocyte; rapid activation of neutral **sphingomyelinase** by hypoxia-reoxygenation of cardiac myocytes)
IT Hypoxia, animal
(rapid activation of neutral **sphingomyelinase** by hypoxia-reoxygenation of cardiac myocytes)
IT Antioxidants
Fibroblast

Oxidative stress, biological
Signal transduction, biological
(rapid activation of neutral **sphingomyelinase** by hypoxia-reoxygenation of cardiac myocytes in relation to)
IT Reactive oxygen species
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(rapid activation of neutral **sphingomyelinase** by hypoxia-reoxygenation of cardiac myocytes in relation to)
IT Oxygenation
(re-; rapid activation of neutral **sphingomyelinase** by hypoxia-reoxygenation of cardiac myocytes)
IT **9031-54-3**, **Sphingomyelinase** C
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(rapid activation of neutral **sphingomyelinase** by hypoxia-reoxygenation of cardiac myocytes)
IT 155215-87-5
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(rapid activation of neutral **sphingomyelinase** by hypoxia-reoxygenation of cardiac myocytes in relation to)
IT 7782-44-7D, Oxygen, radicals, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(rapid activation of neutral **sphingomyelinase** by hypoxia-reoxygenation of cardiac myocytes in relation to)
IT **9031-54-3**, **Sphingomyelinase** C
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(rapid activation of neutral **sphingomyelinase** by hypoxia-reoxygenation of cardiac myocytes)
RN 9031-54-3 HCAPLUS
CN Sphingomyelinase C (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L161 ANSWER 14 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:379636 HCAPLUS
DOCUMENT NUMBER: 133:102835
TITLE: Lysophosphatidic acid and **sphingosine** 1-phosphate: two lipid villains provoking cardiovascular diseases?
AUTHOR(S): Siess, Wolfgang; Essler, Markus; Brandl, Richard
CORPORATE SOURCE: Institut fur Prophylaxe und Epidemiologie der Kreislaufkrankheiten, Klinikum Innenstadt, Universitat Munchen, Munchen, D 80336, Germany
SOURCE: IUBMB Life (**2000**), 49(3), 167-171
CODEN: IULIF8; ISSN: 1521-6543
PUBLISHER: Taylor & Francis
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
ED Entered STN: 08 Jun 2000
AB A review with 51 refs. Lysophosphatidic acid (LPA) and **sphingosine** 1-phosphate (S1P) are potent bioactive lipids with specific and multiple effects on cells of the vessel wall and blood platelets. In this paper we suggest that these lipid mols. are involved

in atherogenesis, pathol. vasoconstriction, plaque rupture, and intravascular thrombus formation, which leads us to propose new strategies for the **prevention** and **therapy** of cardiovascular diseases. The conclusions are hypothetical, in that the studies were so far mainly carried out on isolated cells or cultured cells in vitro and the results were extrapolated to the situation in vivo.

CC 14-0 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 1

ST review lysophosphatidate **sphingosine** phosphate cardiovascular disease atherosclerosis **therapy**

IT Antiarteriosclerotics
(antiatherosclerotics; lysophosphatidic acid and **sphingosine** 1-phosphate in association with **prevention** and **therapy** of atherosclerosis and cardiovascular diseases in human)

IT **Cardiovascular system**
(**disease**; lysophosphatidic acid and **sphingosine** 1-phosphate in association with **prevention** and **therapy** of atherosclerosis and cardiovascular diseases in human)

IT **Blood vessel, disease**
(endothelium, injury; lysophosphatidic acid and **sphingosine** 1-phosphate in association with **prevention** and **therapy** of atherosclerosis and cardiovascular diseases in human)

IT **Atherosclerosis**
Platelet (blood)
Thrombus
Vasoconstriction
(lysophosphatidic acid and **sphingosine** 1-phosphate in association with **prevention** and **therapy** of atherosclerosis and cardiovascular diseases in human)

IT Lysophosphatidic acids
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(lysophosphatidic acid and **sphingosine** 1-phosphate in association with **prevention** and **therapy** of atherosclerosis and cardiovascular diseases in human)

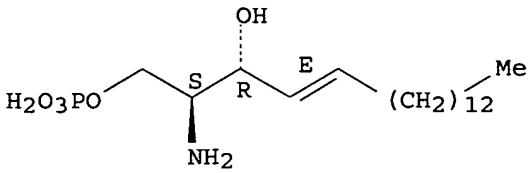
IT **26993-30-6, Sphingosine** 1-phosphate
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(lysophosphatidic acid and **sphingosine** 1-phosphate in association with **prevention** and **therapy** of atherosclerosis and **cardiovascular** diseases in human)

IT **26993-30-6, Sphingosine** 1-phosphate
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(lysophosphatidic acid and **sphingosine** 1-phosphate in association with **prevention** and **therapy** of atherosclerosis and **cardiovascular** diseases in human)

RN 26993-30-6 HCAPLUS

CN 4-Octadecene-1,3-diol, 2-amino-, 1-(dihydrogen phosphate), (2S,3R,4E)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L161 ANSWER 15 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:529160 HCAPLUS
DOCUMENT NUMBER: 131:165335
TITLE: **Sphingolipid** derivatives, their preparation, and their **therapeutic** use
INVENTOR(S): Liotta, Dennis C.; Merrill, Alfred H., Jr.; Keane, Thomas E.; Schmelz, Eva M.; Bhalla, Kapil N.
PATENT ASSIGNEE(S): Emory University, USA
SOURCE: PCT Int. Appl., 140 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
WO 9941266	A1	19990819	WO 1999-US3093		19990212	<--
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN						
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG						
CA 2320117	AA	19990819	CA 1999-2320117		19990212	<--
AU 9927644	A1	19990830	AU 1999-27644		19990212	<--
AU 765809	B2	20031002				
EP 1053243	A1	20001122	EP 1999-908143		19990212	<--
R: DE, FR, GB, IT, IE						
US 6610835	B1	20030826	US 1999-249211		19990212	<--
AU 2003235051	A1	20030911	AU 2003-235051		20030814	<--
US 2004039212	A1	20040226	US 2003-647801		20030825	<--
PRIORITY APPLN. INFO.:			US 1998-74536P	P	19980212	<--
			AU 1999-27644	A3	19990212	<--
			US 1999-249211	A1	19990212	<--
			WO 1999-US3093	W	19990212	<--

OTHER SOURCE(S): MARPAT 131:165335
ED Entered STN: 24 Aug 1999
AB Derivs. of **sphingolipids** (Markush included) are provided. The compds. are useful in the **treatment** of abnormal cell proliferation, including benign and malignant tumors, the promotion of cell differentiation, the induction of apoptosis, the inhibition of protein kinase C, and the **treatment** of inflammatory conditions, psoriasis, inflammatory bowel disease as well as proliferation of smooth muscle cells in the course of development of plaques in vascular tissue. The invention also includes a method for triggering the release of cytochrome c from mitochondria that includes **administering** an effective amount of a **sphingolipid** or its derivative or prodrug to a

host in need thereof. Further, the invention provides a method for **treating** bacterial infections, including those that influence colon cancer and other disorders of the intestine, that includes **administering** an effective amount of one of the active compds. identified herein.

IC ICM C07H015-10
ICS C07F009-08; C07F009-22; A61K031-70; A61K031-66

CC 1-12 (Pharmacology)
Section cross-reference(s): 26, 63

ST **therapeutic sphingolipid** deriv prepn; antiproliferative antitumor cell differentiation **sphingolipid** deriv; protein kinase C **inhibition sphingolipid** deriv; apoptosis antiinflammatory psoriasis **sphingolipid** deriv; inflammatory bowel disease **sphingolipid** deriv; smooth muscle cell proliferation **sphingolipid** deriv; cytochrome c release mitochondria **sphingolipid** deriv; colon cancer bacterial infection **sphingolipid** deriv

IT Clostridium botulinum
(B, neurotoxin; **sphingolipid** derivative preparation and **therapeutic** use)

IT Antitumor agents
(Brenner tumor; **sphingolipid** derivative preparation and **therapeutic** use)

IT Intestine, disease
(Crohn's; **sphingolipid** derivative preparation and **therapeutic** use)

IT Antitumor agents
(Kaposi's sarcoma; **sphingolipid** derivative preparation and **therapeutic** use)

IT Toxins
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(Shiga-like toxin; **sphingolipid** derivative preparation and **therapeutic** use)

IT Skin, neoplasm
Skin, neoplasm
(T-cell lymphoma, **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)

IT Kidney, neoplasm
(Wilms', **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)

IT Prostate gland
Prostate gland
(adenocarcinoma, **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)

IT Antitumor agents
(adenocarcinoma; **sphingolipid** derivative preparation and **therapeutic** use)

IT Fumonisins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(analogs; **sphingolipid** derivative preparation and **therapeutic** use)

IT Ceramides
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(and acylated derivs.; **sphingolipid** derivative preparation and **therapeutic** use)

IT Adenoma

(and fibroadenoma, **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antibiotics
(antibiotic-associated colitis; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
(arrhenoblastoma and hilar cell tumor; **sphingolipid** derivative preparation and **therapeutic** use)
IT Azo compounds
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(azoreductase-**reducible.** fumonisin analog with; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
(bladder carcinoma; **sphingolipid** derivative preparation and **therapeutic** use)
IT Bladder
Bladder
(carcinoma, **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Musculoskeletal diseases
(cartilage chondrosarcoma, **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Toxins
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(cholera; **sphingolipid** derivative preparation and **therapeutic** use)
IT Cartilage
Cartilage
(chondrosarcoma, **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
(chondrosarcoma; **sphingolipid** derivative preparation and **therapeutic** use)
IT Chorion
Chorion
(choriocarcinoma, **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
(choriocarcinoma; **sphingolipid** derivative preparation and **therapeutic** use)
IT Intestine, disease
(colitis, antibiotic-associated; **sphingolipid** derivative preparation and **therapeutic** use)
IT Microorganism
(colon cancer-influencing microflora colonization; **sphingolipid** derivative preparation and **therapeutic** use)
IT Intestine, neoplasm
(colon, colon cancer-influencing microflora colonization; **sphingolipid** derivative preparation and **therapeutic** use)
IT Intestine
(colon, crypt cell; **sphingolipid** derivative preparation and **therapeutic** use)
IT Intestine, neoplasm
Intestine, neoplasm
(colon, **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
(colon; **sphingolipid** derivative preparation and **therapeutic**

use)
IT Intestine, disease
(enteritis, lower bowel; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
(erythroleukemia; **sphingolipid** derivative preparation and **therapeutic** use)
IT Reproductive tract
(female, disease, premalignant; **sphingolipid** derivative preparation and **therapeutic** use)
IT Neoplasm
(fibroma, and chondroma and osteoma, **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
(fibrosarcoma; **sphingolipid** derivative preparation and **therapeutic** use)
IT TCR (T cell receptors)
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fragments and variable regions, **sphingolipid** derivative conjugates; **sphingolipid** derivative preparation and **therapeutic** use)
IT Amino acids, biological studies
Fructooligosaccharides
Peptides, biological studies
Phosphates, biological studies
Proteins, general, biological studies
Sulfonates
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fumonisin analog with; **sphingolipid** derivative preparation and **therapeutic** use)
IT Mycosis
(fungoides; **sphingolipid** derivative preparation and **therapeutic** use)
IT Carbohydrates, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(furanose/pyranose-containing, fumonisin analog with; **sphingolipid** derivative preparation and **therapeutic** use)
IT Drugs
(gastrointestinal; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
Antitumor agents
(genitourinary tract tumor **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Neuroglia
Neuroglia
(glioma, **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
(glioma; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
(granulosa cell tumor, granulosa-theca; **sphingolipid** derivative preparation and **therapeutic** use)

IT Ovary, neoplasm
Ovary, neoplasm
(granulosa cell tumor, **inhibitors**, granulosa-theca; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
(hemangioma, and lymphangioma **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT **Blood vessel, neoplasm**
Blood vessel, neoplasm
(hemangioma, **inhibitors**, and lymphangioma **inhibitors** ; **sphingolipid** derivative preparation and **therapeutic** use)
IT **Blood vessel, neoplasm**
Blood vessel, neoplasm
(hemangiosarcoma, **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
(hemangiosarcoma; **sphingolipid** derivative preparation and **therapeutic** use)
IT Neoplasm
(hydatidiform mole, **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Intestine, disease
(ileocecitis; **sphingolipid** derivative preparation and **therapeutic** use)
IT Cell differentiation
(**inducers**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Intestine, disease
(inflammatory; **sphingolipid** derivative preparation and **therapeutic** use)
IT Intestine, neoplasm
Intestine, neoplasm
Papilloma
Papilloma
Skin, neoplasm
Skin, neoplasm
(**inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Animal tissue
(interstitial, interstitial cell tumor **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
Antitumor agents
(intestine; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
(leiomyoma **inhibitors**, and rhabdomyoma **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Myoma
Myoma
(leiomyoma, **inhibitors**, and rhabdomyoma **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
(leiomyosarcoma; **sphingolipid** derivative preparation and **therapeutic** use)
IT Adipose tissue, neoplasm
Adipose tissue, neoplasm
(lipoma, **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents

(lipoma; **sphingolipid** derivative preparation and **therapeutic** use)
IT Adipose tissue, neoplasm
Adipose tissue, neoplasm
(liposarcoma, **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
(liposarcoma; **sphingolipid** derivative preparation and **therapeutic** use)
IT Lymphatic system
Lymphatic system
(lymphangiosarcoma, **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
(lymphangiosarcoma; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
(mammary gland; **sphingolipid** derivative preparation and **therapeutic** use)
IT Meninges
Meninges
(meningioma, **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
(meningioma; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
(multiple myeloma; **sphingolipid** derivative preparation and **therapeutic** use)
IT Skin, neoplasm
(mycosis fungoides; **sphingolipid** derivative preparation and **therapeutic** use)
IT Leukemia
(myelogenous, **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Reproductive tract
(neoplasm, female; **sphingolipid** derivative preparation and **therapeutic** use)
IT Mammary gland
Mammary gland
(neoplasm, **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
(neuroma **inhibitors**, and ganglioneuroma **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Nerve, neoplasm
Nerve, neoplasm
(neuroma, **inhibitors**, and ganglioneuroma **inhibitors** ; **sphingolipid** derivative preparation and **therapeutic** use)
IT Toxins
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(neurotoxins, Clostridium botulinum type B; **sphingolipid** derivative preparation and **therapeutic** use)
IT Skin, disease
(nevus; **sphingolipid** derivative preparation and **therapeutic** use)
IT Bone, neoplasm
Bone, neoplasm
(osteosarcoma, **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)

IT Antitumor agents
(osteosarcoma; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
Antitumor agents
(papilloma **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Polyamides, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(poly(amino acids), fumonisin analog with; **sphingolipid** derivative preparation and **therapeutic** use)
IT Intestine, neoplasm
(polyp, intestinal; **sphingolipid** derivative preparation and **therapeutic** use)
IT Mucous membrane
(pre-malignant disease and neoplasm **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Disease, animal
(preneoplastic lesions; **sphingolipid** derivative preparation and **therapeutic** use)
IT **Enzymes, biological studies**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(prodrug cleavable by; **sphingolipid** derivative preparation and **therapeutic** use)
IT Drug delivery systems
(prodrugs; **sphingolipid** derivative preparation and **therapeutic** use)
IT Proliferation **inhibition**
(proliferation **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
(prostate adenocarcinoma; **sphingolipid** derivative preparation and **therapeutic** use)
IT Intestine, disease
(pseudomembranous enterocolitis; **sphingolipid** derivative preparation and **therapeutic** use)
IT Ligands
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(receptor-binding, **sphingolipid** derivative conjugates; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
(rhabdomyosarcoma; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
(sarcoma, meningeal sarcoma and cystosarcoma phyllodes; **sphingolipid** derivative preparation and **therapeutic** use)
IT Schwann cell
(schwannoma; **sphingolipid** derivative preparation and **therapeutic** use)
IT Mesenchyme
(sex cord; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antitumor agents
(skin T-cell lymphoma; **sphingolipid** derivative preparation and **therapeutic** use)

IT Antitumor agents
Antitumor agents
(skin; **sphingolipid** derivative preparation and **therapeutic** use)
IT Antibodies
Antigens
Hormone receptors
Hormones, animal, biological studies
Receptors
Steroids, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**sphingolipid** derivative conjugates; **sphingolipid** derivative preparation and **therapeutic** use)
IT Anti-inflammatory agents
Antibacterial agents
Antimicrobial agents
Antirheumatic agents
Antitumor agents
Antiviral agents
Borrelia burgdorferi
Candida albicans
Chemotherapy
Cytotoxic agents
Dermatomyositis
Drug targeting
Escherichia coli
Fungicides
Haemophilus influenzae
Helicobacter pylori
Human immunodeficiency virus
Influenza virus
Intestine, disease
Molluscum contagiosum virus
Pheochromocytoma
Pseudomonas aeruginosa
Psoriasis
Sendai virus
(**sphingolipid** derivative preparation and **therapeutic** use)
IT **Sphingolipids**
Sphingomyelins
Sphingosines
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**sphingolipid** derivative preparation and **therapeutic** use)
IT Carbohydrates, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**sphingolipid** derivative preparation and **therapeutic** use)
IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**sphingolipid**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Neoplasm
(teratoma, **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)
IT Thymus gland
Thymus gland

(thymoma, **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)

IT Antitumor agents
(thymoma; **sphingolipid** derivative preparation and **therapeutic** use)

IT Urogenital tract
Urogenital tract
(tumor **inhibitors**; **sphingolipid** derivative preparation and **therapeutic** use)

IT Intestine, disease
(ulcerative colitis; **sphingolipid** derivative preparation and **therapeutic** use)

IT 9029-31-6, Azoreductase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(azo bond-containing moiety **reducible** by; **sphingolipid** derivative preparation and **therapeutic** use)

IT 3082-95-9P 4201-55-2P 4201-60-9P 7355-18-2P 61362-77-4P
63478-76-2P, 6-Heptyn-1-ol 73448-13-2P 92420-89-8P 102308-32-7P
108149-60-6P 115464-01-2P 119837-81-9P 119837-87-5P 128098-41-9P
131606-77-4P 132260-32-3P 152565-02-1P 153004-34-3P 238429-67-9P
238429-68-0P 238429-69-1P 238429-70-4P 238429-71-5P 238429-72-6P
238429-74-8P 238429-76-0P 238429-77-1P 238429-78-2P 238429-80-6P
238429-81-7P 238429-83-9P 238429-84-0P 238429-85-1P 238757-59-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction; **sphingolipid** derivative preparation and **therapeutic** use)

IT 98-88-4, Benzoyl chloride 108-24-7, Acetic anhydride 112-67-4, Palmitoyl chloride 545-06-2, Trichloroacetonitrile 623-65-4, Palmitic anhydride 629-05-0, 1-Octyne 765-10-6, 1-Tetradecyne 765-13-9, 1-Pentadecyne 871-91-0, 7-Octyn-1-ol 928-90-5, 5-Hexyn-1-ol 2766-43-0 2774-84-7, 10-Undecyn-1-ol 2834-00-6, 2-Pentadecyn-1-ol 5390-04-5, 4-Pentyn-1-ol 5921-73-3, 2-Nonyn-1-ol 10160-28-8, 8-Nonyn-1-ol 14916-79-1, 3-Heptyn-1-ol 14916-80-4, 3-Octyn-1-ol 18162-48-6 18202-10-3, 11-Dodecyn-1-ol 18202-13-6, 14-Pentadecyn-1-ol 30525-89-4, Paraformaldehyde 32449-92-6, D-Glucuronolactone 55357-38-5, Choline tosylate 58944-42-6, 5-Heptyn-1-ol 71084-08-7, 9-Dodecyn-1-ol 116355-83-0, Fumonisin B1 125348-17-6 145040-09-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction; **sphingolipid** derivative preparation and **therapeutic** use)

IT 9007-43-6, Cytochrome c, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(release; **sphingolipid** derivative preparation and **therapeutic** use)

IT 9005-25-8, Starch, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(resistant, fumonisin analog with; **sphingolipid** derivative preparation and **therapeutic** use)

IT 9001-45-0, β-Glucuronidase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**sphingolipid** derivative preparation and **therapeutic** use)

IT 238429-86-2P 238429-87-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);

BIOL (Biological study); PREP (Preparation); USES (Uses)
(**sphingolipid** derivative preparation and **therapeutic** use)

IT 63-42-3D, Lactose, fumonisin analog with 107-73-3D, Phosphocholine, fumonisin analog with 110-15-6D, Succinic acid, fumonisin analog with dextran linked by, biological studies 110-94-1D, Glutaric acid, fumonisin analog with dextran linked by 407-41-0D, fumonisin analog with 470-55-3D, Stachyose, fumonisin analog with 492-61-5D, β-D-Glucopyranose, fumonisin analog with 512-69-6D, Raffinose, fumonisin analog with **764-22-7**, Sphinganine **764-22-7D**, Sphinganine, acylated derivs. 1071-23-4D, Phosphoethanolamine, fumonisin analog with 2238-89-3 2238-89-3D, derivs. 2238-90-6 2238-90-6D, derivs. 5966-29-0 5966-29-0D, acylated derivs. 7296-15-3D, α-D-Mannopyranose, fumonisin analog with 7296-64-2D, β-D-Galactopyranose, fumonisin analog with 7585-39-9D, β-Cyclodextrin, amides and esters, fumonisin analog with 9004-54-0D, Dextran, fumonisin analog with succinate or glutarate-linked, biological studies 13360-52-6D, fumonisin analog with 14131-68-1D, fumonisin analog with 23018-83-9D, β-D-Glucopyranuronic acid, fumonisin analog with 23214-92-8, Doxorubicin 34324-89-5 34324-89-5D, derivs. 52050-17-6D, derivs. 54947-67-0 54947-67-0D, derivs. 74365-77-8D, derivs. 105561-73-7D, derivs. 151589-95-6 238429-50-0 238429-51-1 238429-52-2 238429-53-3 238429-54-4 238429-56-6 238429-56-6D, derivs. 238429-57-7 238429-58-8 238429-59-9 238429-60-2 238429-61-3 238429-62-4 238429-63-5 238429-64-6 238429-65-7D, derivs. 238429-66-8D, derivs. 238757-36-3 238757-40-9 238757-45-4 238757-49-8 238757-52-3 238757-55-6D, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**sphingolipid** derivative preparation and **therapeutic** use)

IT 141436-78-4, Protein kinase C
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**sphingolipid** derivative preparation and **therapeutic** use)

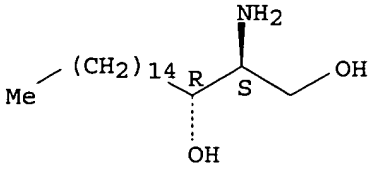
IT 238429-82-8P
RL: BYP (Byproduct); PREP (Preparation)
(**sphingolipid** derivative preparation and **therapeutic** use)

IT 54353-31-0P 58909-84-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(**sphingolipid** derivative preparation and **therapeutic** use)

IT **764-22-7**, Sphinganine **764-22-7D**, Sphinganine, acylated derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**sphingolipid** derivative preparation and **therapeutic** use)

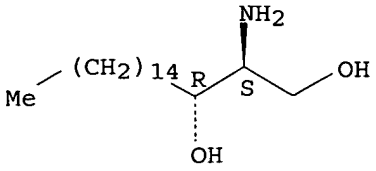
RN 764-22-7 HCAPLUS
CN 1,3-Octadecanediol, 2-amino-, (2S,3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 764-22-7 HCAPLUS
CN 1,3-Octadecanediol, 2-amino-, (2S,3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L161 ANSWER 16 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:193987 HCAPLUS
DOCUMENT NUMBER: 130:232524
TITLE: A method of modulating cellular activity
INVENTOR(S): Vadas, Mathew; Gamble, Jennifer; Xia, Pu; Barter, Philip; Rye, Kerry-Anne; Wattenberg, Brian; Pitson, Stuart
PATENT ASSIGNEE(S): Medvet Science Pty. Ltd., Australia
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9912533	A1	19990318	WO 1998-AU730	19980908 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2302838	AA	19990318	CA 1998-2302838	19980908 <--
AU 9889658	A1	19990329	AU 1998-89658	19980908 <--
AU 757358	B2	20030220		
EP 1011654	A1	20000628	EP 1998-941157	19980908 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001515857	T2	20010925	JP 2000-510431	19980908 <--
US 2002051777	A1	20020502	US 2001-977217	20011016 <--
US 6649362	B2	20031118		
US 2005074830	A1	20050407	US 2003-679485	20031007 <--
AU 2006200646	A1	20060309	AU 2006-200646	20060216 <--

PRIORITY APPLN. INFO.:		
AU 1997-9002	A	19970908 <--
AU 1998-89658	A3	19980908 <--
WO 1998-AU730	W	19980908 <--
US 2000-508249	A1	20000601 <--
US 2001-977217	A3	20011016
AU 2003-204254	A3	20030519

ED Entered STN: 25 Mar 1999

AB The present invention relates generally to a method of modulating cellular activity and agents useful for same. More particularly, the present invention contemplates a method of modulating endothelial cell activity and even more particularly endothelial cell adhesion mol. expression. Most particularly, the present invention provides a method of **treating** conditions involving inflammatory mechanisms such as coronary heart disease by **preventing** or reducing endothelial cell adhesion mol. expression. One aspect of the invention is **administration** of an agent which **modulates** one or more components of the **sphingosine** kinase signaling pathway (such as **sphingosine** kinase or **sphingosine**-1-phosphate). The **inhibitory effect** of high-d. lipoproteins (HDL) on the **sphingosine** kinase signaling pathway was determined A further aspect of the invention is a method for detecting **sphingosine** kinase activity using 33P-ATP and **sphingosine** in the presence of a scintillant.

IC ICM A61K031-13
ICS A61K035-14; A61K038-00

CC 1-12 (Pharmacology)

ST endothelial cell adhesion mol expression inhibition; **sphingosine** kinase signaling pathway **inhibition**; coronary heart disease adhesion mol modulation

IT Selectins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(E-; cellular activity response to **modulating** endothelial cell adhesion mol. expression and **sphingosine** kinase signaling pathway using agents such as HDL in relation to **treatment** of inflammatory conditions such as coronary heart disease)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NF-κB (nuclear factor κB); cellular activity response to **modulating** endothelial cell adhesion mol. expression and **sphingosine** kinase signaling pathway using agents such as HDL in relation to **treatment** of inflammatory conditions such as coronary heart disease)

IT Cell adhesion molecules
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(PECAM-1; cellular activity response to **modulating** endothelial cell adhesion mol. expression and **sphingosine** kinase signaling pathway using agents such as HDL in relation to **treatment** of inflammatory conditions such as coronary heart disease)

IT Cell adhesion molecules
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(VCAM-1; cellular activity response to **modulating** endothelial cell adhesion mol. expression and **sphingosine** kinase signaling pathway using agents such as HDL in relation to **treatment** of inflammatory conditions such as coronary heart disease)

IT Anti-inflammatory agents
Signal transduction, biological
(cellular activity response to **modulating** endothelial cell adhesion mol. expression and **sphingosine** kinase signaling pathway using agents such as HDL in relation to **treatment** of inflammatory conditions such as coronary heart disease)

IT Cell adhesion molecules
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cellular activity response to **modulating** endothelial cell adhesion mol. expression and **sphingosine** kinase signaling pathway using agents such as HDL in relation to **treatment** of inflammatory conditions such as coronary heart disease)

IT **Artery, disease**
(coronary; cellular activity response to **modulating** endothelial cell adhesion mol. expression and **sphingosine** kinase signaling pathway using agents such as HDL in relation to **treatment** of inflammatory conditions such as coronary heart disease)

IT Blood vessel
(endothelium; cellular activity response to **modulating** endothelial cell adhesion mol. expression and **sphingosine** kinase signaling pathway using agents such as HDL in relation to **treatment** of inflammatory conditions such as coronary heart disease)

IT Ceramides
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(formation; cellular activity response to **modulating** endothelial cell adhesion mol. expression and **sphingosine** kinase signaling pathway using agents such as HDL in relation to **treatment** of inflammatory conditions)

IT Lipoproteins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(high-d., 3; cellular activity response to **modulating** endothelial cell adhesion mol. expression and **sphingosine** kinase signaling pathway using agents such as HDL in relation to **treatment** of inflammatory conditions such as coronary heart disease)

IT **Sphingomyelins**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(hydrolysis; cellular activity response to **modulating** endothelial cell adhesion mol. expression and **sphingosine** kinase signaling pathway using agents such as HDL in relation to **treatment** of inflammatory conditions)

IT Scintillation
(in **sphingosine** kinase determination; cellular activity response to **modulating** endothelial cell adhesion mol. expression and **sphingosine** kinase signaling pathway using agents such as HDL)

IT **50864-48-7, Sphingosine** kinase
RL: ANT (Analyte); BPR (Biological process); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PROC (Process)
(cellular activity response to **modulating** endothelial cell adhesion mol. expression and **sphingosine** kinase signaling pathway using agents such as HDL in relation to **treatment** of inflammatory conditions such as coronary heart disease)

IT 119567-63-4, N,N-**Dimethylsphingosine**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cellular activity response to **modulating** endothelial cell

adhesion mol. expression and **sphingosine** kinase signaling pathway using agents such as HDL in relation to **treatment** of inflammatory conditions such as coronary heart disease)

IT **26993-30-6**, **Sphingosine**-1-phosphate 142243-02-5, ERK kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cellular activity response to **modulating** endothelial cell adhesion mol. expression and **sphingosine** kinase signaling pathway using agents such as HDL in relation to **treatment** of inflammatory conditions such as **coronary heart** disease)

IT 133587-41-4
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(in **sphingosine** kinase determination; cellular activity response to **modulating** endothelial cell adhesion mol. expression and **sphingosine** kinase signaling pathway using agents such as HDL)

IT **50864-48-7**, **Sphingosine** kinase
RL: ANT (Analyte); BPR (Biological process); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PROC (Process)
(cellular activity response to **modulating** endothelial cell adhesion mol. expression and **sphingosine** kinase signaling pathway using agents such as HDL in relation to **treatment** of inflammatory conditions such as coronary heart disease)

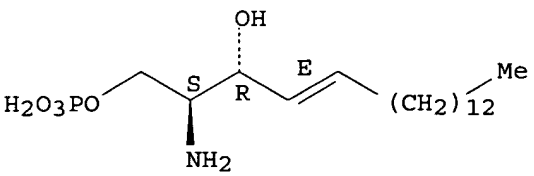
RN 50864-48-7 HCAPLUS
CN Kinase (phosphorylating), dihydrosphingosine (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **26993-30-6**, **Sphingosine**-1-phosphate
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cellular activity response to **modulating** endothelial cell adhesion mol. expression and **sphingosine** kinase signaling pathway using agents such as HDL in relation to **treatment** of inflammatory conditions such as **coronary heart** disease)

RN 26993-30-6 HCAPLUS
CN 4-Octadecene-1,3-diol, 2-amino-, 1-(dihydrogen phosphate), (2S,3R,4E)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L161 ANSWER 17 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:681719 HCAPLUS
DOCUMENT NUMBER: 132:176814
TITLE: Sequence of cardiovascular changes leading to pulmonary edema in swine fed culture material

containing fumonisin

AUTHOR(S): Smith, Geoffrey W.; Constable, Peter D.; Tumbleson, Mike E.; Rottinghaus, George E.; Haschek, Wanda M.
CORPORATE SOURCE: Departments of Veterinary Pathobiology, University of Illinois, Urbana, IL, 61802, USA

SOURCE: American Journal of Veterinary Research (**1999**), 60(10), 1292-1300
CODEN: AJVRAH; ISSN: 0002-9645
PUBLISHER: American Veterinary Medical Association
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 27 Oct 1999

AB Objectives-To determine the sequence of cardiovascular and blood gas changes induced by ingestion of fumonisin-containing culture material in swine and to examine the temporal relationship of these changes to plasma sphinganine and **sphingosine** concns. Animals-12 healthy castrated pigs (38 to 50 kg). Procedure-Pigs were instrumented to permit cardiovascular monitoring and collection of blood samples. Baseline values were obtained, and pigs were randomly assigned to 1 of 2 groups. Control pigs (n = 6) were fed a standard grower diet, whereas culture material that contained 20 mg of fumonisin B1/kg of body weight was added to the feed of **treated** pigs (n = 6) each day. Hemodynamic data, results of arterial and mixed venous blood gas analyses, and plasma sphinganine and **sphingosine** concns. were recorded every 12 h until **treated** pigs were euthanatized because of impending death from pulmonary edema. Results-Sphinganine and **sphingosine** concns. were increased in plasma of **treated** pigs within 24 h of initial fumonisin exposure and continued to increase dramatically until euthanasia. Fumonisin-**treated** pigs had increased respiratory rate, mean pulmonary artery pressure, and pulmonary artery wedge pressure, along with decreased heart rate and cardiac output in the 12-h period before euthanasia. Fumonisin-**treated** pigs also had systemic arterial hypotension, arterial and mixed venous hypoxemia, metabolic acidosis, decreased oxygen delivery, and increased oxygen consumption immediately before euthanasia. Conclusions and Clin. Relevance-Fumonisin-induced pulmonary edema in swine is probably caused by acute left-sided heart failure. Onset of hemodynamic changes was associated with plasma sphinganine concentration ≥ 2.2 μM/L and plasma **sphingosine** concentration ≥ 1 μM/L.

CC 4-5 (Toxicology)

IT Lung, disease
(edema; sequence of cardiovascular changes leading to pulmonary edema in swine fed culture material containing fumonisin in relation to **sphingosine** and sphinganine concns.)

IT **Heart, disease**
(failure, left-sided heart failure; sequence of cardiovascular changes leading to pulmonary edema in swine fed culture material containing fumonisin in relation to **sphingosine** and sphinganine concns.)

IT Blood vessel
Blood vessel
(permeability; sequence of cardiovascular changes leading to pulmonary edema in swine fed culture material containing fumonisin in relation to **sphingosine** and sphinganine concns.)

IT Biological transport
(permeation, vascular; sequence of cardiovascular changes leading to pulmonary edema in swine fed culture material containing fumonisin in relation to **sphingosine** and sphinganine concns.)

IT Cardiovascular system
Swine
(sequence of cardiovascular changes leading to pulmonary edema in swine fed culture material containing fumonisin in relation to

sphingosine and sphinganine concns.)

IT Fumonisins
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(sequence of cardiovascular changes leading to pulmonary edema in swine fed culture material containing fumonisin in relation to **sphingosine** and sphinganine concns.)

IT **Sphingosines**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(sequence of **cardiovascular** changes leading to pulmonary edema in swine fed culture material containing fumonisin in relation to **sphingosine** and sphinganine concns.)

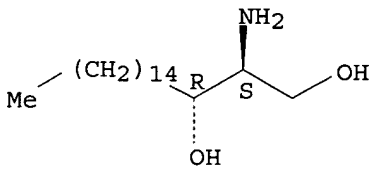
IT 116355-83-0, Fumonisin B1
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(sequence of cardiovascular changes leading to pulmonary edema in swine fed culture material containing fumonisin in relation to **sphingosine** and sphinganine concns.)

IT **764-22-7**, Sphinganine
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(sequence of **cardiovascular** changes leading to pulmonary edema in swine fed culture material containing fumonisin in relation to **sphingosine** and sphinganine concns.)

IT **764-22-7**, Sphinganine
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(sequence of **cardiovascular** changes leading to pulmonary edema in swine fed culture material containing fumonisin in relation to **sphingosine** and sphinganine concns.)

RN 764-22-7 HCAPLUS
CN 1,3-Octadecanediol, 2-amino-, (2S,3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L161 ANSWER 18 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:539093 HCAPLUS
DOCUMENT NUMBER: 129:300612
TITLE: Arterial-wall **sphingomyelinase** and atherogenesis
AUTHOR(S): Tabas, Ira; Schissel, Scott L.; Williams, Kevin Jon; Schuchman, Edward H.; Rapp, Joseph H.; Tweedie-Hardman, Judith
CORPORATE SOURCE: Departments of Anatomy and Cell Biology and Medicine, Columbia University, New York, NY, USA
SOURCE: International Congress Series (**1998**), 1155(Atherosclerosis XI), 895-901
CODEN: EXMDA4; ISSN: 0531-5131
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; **General Review**

LANGUAGE: English
ED Entered STN: 26 Aug 1998
AB A review with 31 refs. The subendothelial retention and aggregation of atherogenic lipoproteins are key events in atherogenesis. Lipoprotein aggregation leads to massive macrophage foam cell formation and further promotes lipoprotein retention. The authors have probed one potential mechanism of lesional lipoprotein aggregation, namely hydrolysis of lesional lipoproteins by the enzyme **sphingomyelinase** (SMase). Plasma and lesional lipoproteins were analyzed directly for ceramide content or incubated in vitro with bacterial SMase, rabbit aortic strips or SMase isolated from the conditioned medium of cultured cells, and then assayed for ceramide and lipoprotein aggregation. **Treatment** of LDL with a bacterial SMase led to the formation of LDL aggregates that appeared similar to those that form in lesions (that greatly enhance lipoprotein retention to matrix and that are able to induce massive macrophage foam cell formation). The mechanism involves the generation of lipoprotein-ceramide. Most importantly, aggregated LDL isolated from human lesions (but not unaggregated lesional LDL or plasma LDL) was enriched in ceramide, indicating action by an arterial-wall SMase. Furthermore, when (3H)SM-labeled LDL was incubated with strips of rabbit aorta ex vivo, (3H)ceramide was increased in the retained (but not the unretained) LDL. As a potential source of extracellular SMase in lesions, cultured macrophages and endothelial cells were found to secrete a SMase activity (S-SMase) that can hydrolyze and aggregate atherogenic lipoproteins. Lipoproteins in lesions are hydrolyzed by an arterial-wall SMase, a process that might promote lipoprotein aggregation, enhanced lipoprotein retention and macrophage foam cell formation. A leading candidate for this arterial-wall SMase is S-SMase, which secreted by macrophages and endothelial cells can hydrolyze and aggregate atherogenic lipoproteins.
CC 14-0 (Mammalian Pathological Biochemistry)
ST review **sphingomyelinase** LDL lipoprotein atherosclerosis
IT Artery
Atherosclerosis
(arterial wall **sphingomyelinase** hydrolysis of lipoproteins in atherosclerosis)
IT **Sphingomyelins**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**arterial** wall **sphingomyelinase** hydrolysis of lipoproteins in atherosclerosis)
IT Macrophage
(arterial wall **sphingomyelinase** hydrolysis of lipoproteins in atherosclerosis in relation to)
IT Artery
(foam cell; arterial wall **sphingomyelinase** hydrolysis of lipoproteins in atherosclerosis in relation to)
IT Lipoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(low-d.; arterial wall **sphingomyelinase** hydrolysis of lipoproteins in atherosclerosis)
IT Ceramides
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(**sphingomyelinase effect** lipoprotein content of ceramide in atherogenesis)
IT **9031-54-3, Sphingomyelinase** C
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(arterial wall **sphingomyelinase** hydrolysis of lipoproteins in

atherosclerosis)
IT **9031-54-3**, **Sphingomyelinase** C
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(arterial wall **sphingomyelinase** hydrolysis of lipoproteins in atherosclerosis)
RN 9031-54-3 HCAPLUS
CN Sphingomyelinase C (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L161 ANSWER 19 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:619955 HCAPLUS
DOCUMENT NUMBER: 130:60916
TITLE: L-Threo-1-phenyL-2-decanoylamino-3-morpholino-1-propanol stimulates ganglioside biosynthesis, neurite outgrowth and synapse formation in cultured cortical neurons, and ameliorates memory deficits in ischemic rats
AUTHOR(S): Inokuchi, Jin-Ichi; Kuroda, Yoichiro; Kosaka, Shinichi; Fujiwara, Michihiro
CORPORATE SOURCE: Seikagaku Corporation, Tokyo Research Institute, Tokyo, Japan
SOURCE: Acta Biochimica Polonica (**1998**), 45(2), 479-492
CODEN: ABPLAF; ISSN: 0001-527X
PUBLISHER: Polish Biochemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 01 Oct 1998
AB To address the role of brain gangliosides in synaptic plasticity, the synthetic ceramide analog, 1-phenyL-2-decanoylamino-3-morpholino-1-propanol (PDMP) was used to manipulate the biosynthesis of gangliosides in cultured cortical neurons. Spontaneous synchronized oscillatory activity of intracellular Ca2+ between the neurons, which represents synapse formation, was suppressed by the depletion of endogenous gangliosides by D-threo-PDMP, an inhibitor of glucosylceramide synthase. The decreased functional synapse formation was normalized by supplementation of GQ1b but not by the other gangliosides, suggesting that de novo synthesis of ganglioside GQ1b is essential for the synaptic activity (Mizutani A. et al., Biochem. Biophys. Res. Commun. 222, 494-498, 1996). On the other hand, the enantiomer of the **inhibitor**, L-threo-PDMP, could elevate cellular levels of **glycosphingolipids** including gangliosides. This paper presents our recent findings on the neurotrophic actions of L-threo-PDMP in vitro and in vivo. We found that L-PDMP could up-regulate neurite outgrowth, functional synapse formation and ganglioside biosynthesis through activating GM3, GD3 and GQ1b synthases. Simultaneously, the activity of p42 mitogen-activated protein kinase was also facilitated by L-PDMP. To evaluate the efficacy of this drug on long term memory, rats were trained for 2 wk using an 8-arm radial maze task, and then forebrain ischemia was induced by 4-vessel occlusion (for 10 min + 2 with a 60 min interval). Repeated **treatment** of L-threo-PDMP (40 mg/kg, i.p. for 6 days, twice a day) starting 24 h after the ischemia, improved the deficit of the welL-learned spatial memory, demonstrating the potential **therapeutic** use of the ceramide analog for **treatment** of neurodegenerative disorders.
CC 1-11 (Pharmacology)
Section cross-reference(s): 13, 14
IT **Gangliosides**

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ceramide analog L-threo-PDMP stimulates ganglioside biosynthesis, neurite outgrowth and synapse formation in cortical neurons, and ameliorates memory deficits in **ischemic** rats)

IT **Brain, disease**
(ischemia; **ceramide** analog L-threo-PDMP stimulates ganglioside biosynthesis, neurite outgrowth and synapse formation in cortical neurons, and ameliorates memory deficits in ischemic rats)

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L161 ANSWER 20 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:544887 HCAPLUS
DOCUMENT NUMBER: 129:197478
TITLE: New **therapeutic** prospects for the **glycosphingolipid** lysosomal storage diseases
AUTHOR(S): Platt, Frances M.; Butters, Terry D.
CORPORATE SOURCE: Glycobiology Institute, Department of Biochemistry, University of Oxford, Oxford, OX1 3QU, UK
SOURCE: Biochemical Pharmacology (**1998**), 56(4), 421-430
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
ED Entered STN: 27 Aug 1998
AB A review with 50 refs. is given. The **glycosphingolipid** (GSL) lysosomal storage diseases result from mutations in the genes that encode the enzymes required for **glycosphingolipid** catabolism within lysosomes. They are relatively rare diseases, but are frequently severe in terms of their pathol. Many involve progressive neurodegeneration, and in the most severe forms result in death in early infancy. The **therapeutic** options for **treating** these diseases are limited, and for the majority of these disorders there are currently no **therapies** available. To date, most research has focused on correcting the genetic lesion by gene **therapy** or by augmenting the enzyme activity deficient in these patients by introducing fully functional enzyme. This can be achieved by bone marrow transplantation or i.v. infusion of purified or recombinant enzyme (enzyme replacement). Gene **therapy** and enzyme replacement **therapy** are disease specific, and **pharmacol.** approaches for the **treatment** of these disorders have not been fully explored. In this commentary, the problems associated with disease **therapy** are discussed, and a **pharmacol.** agent (N-butyldeoxynojirimycin) is presented for the potential generic **treatment** of this family of disorders. Successful **prevention** of **glycosphingolipid** storage in a mouse model of Tay-Sachs disease suggests that this strategy merits clin. evaluation.
CC 1-0 (Pharmacology)
Section cross-reference(s): 14
ST review **glycosphingolipids** lysosomal storage disease **therapy**
IT **Gangliosidosis**
(Tay-Sachs disease; **therapy** of **glycosphingolipid** lysosomal storage diseases)
IT Gene **therapy**
Lysosomal storage disease
(**therapy** of **glycosphingolipid** lysosomal storage diseases)

IT **Glycosphingolipids**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**therapy** of **glycosphingolipid** lysosomal storage diseases)
IT **Enzymes, biological studies**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**therapy** of **glycosphingolipid** lysosomal storage diseases)
IT 72599-27-0, N-Butyldeoxynojirimycin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**therapy** of **glycosphingolipid** lysosomal storage diseases)
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L161 ANSWER 21 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:94433 HCAPLUS
DOCUMENT NUMBER: 124:142771
TITLE: In vitro accumulation of glucocerebroside in neuroblastoma cells: a model for study of Gaucher disease pathobiology
AUTHOR(S): Prence, E. M.; Chaturvedi, P.; Newburg, D. S.
CORPORATE SOURCE: Div. Med. Genet., Shriver Cent. Mental Retardation, Waltham, MA, 02254, USA
SOURCE: Journal of Neuroscience Research (**1996**), 43(3), 365-71
CODEN: JNREDK; ISSN: 0360-4012
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 14 Feb 1996
AB Gaucher disease is the most common lysosomal **glycosphingolipid** storage disease; decreased activity of glucosylceramide β-glucosidase (GCase) results in the accumulation of glucocerebroside (GlcCer) in macrophage-derived cells. The most devastating types of Gaucher disease also involve neuronopathol., thought to be mediated by intracellular GlcCer accumulation in the brain. In this study, the authors developed an in vitro neuronal cell model for accumulation of endogenous GlcCer to enable studies on the cellular basis for the neuronopathol. of this disease. A human neuroblastoma cell line (SH-SY5Y) was selected because it produced appreciable GCase. When these cells were **treated** with conduritol B epoxide (CBE), a competitive, irreversible inhibitor of this enzyme, GCase levels fell precipitously, while other lysosomal hydrolase levels were unaffected. Relative to untreated control cells, the CBE-**treated** cells accumulated higher levels of GlcCer, but not other related glycolipids, over time. Thus, this in vitro system displayed many essential biol. parameters relevant for studies on cellular events responsible for the neurol. damage that occurs in some types of Gaucher disease. This model should also be useful in investigations of the normal role of **sphingolipids** in neuronal cell function.
CC 14-14 (Mammalian Pathological Biochemistry)
IT **Brain, disease**
Gaucher's disease
(glucocerebroside accumulation by inhibition of **glucosylceramide** β-glucosidase in neuroblastoma cells as model for neuronopathic aspects of Gaucher disease)
IT **Glycosphingolipids**

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**glucocerebroside** accumulation by **inhibition** of glucosylceramide β-glucosidase in neuroblastoma cells as model for neuronopathic aspects of Gaucher disease)

IT **85305-87-9, Glucocerebroside**
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(accumulation of **glucocerebroside** by inhibition of glucosylceramide β-glucosidase in neuroblastoma cells as model for neuronopathic aspects of Gaucher disease)

IT **85305-87-9, Glucocerebroside**
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(accumulation of **glucocerebroside** by inhibition of glucosylceramide β-glucosidase in neuroblastoma cells as model for neuronopathic aspects of Gaucher disease)

RN 85305-87-9 HCAPLUS
CN Ceramide, 1-O-β-D-glucopyranosyl- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L161 ANSWER 22 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:503078 HCAPLUS
DOCUMENT NUMBER: 121:103078
TITLE: Purified ceramide-activated protein kinase, assay for identifying agents which act on same, and methods of using said agents
INVENTOR(S): Kolesnick, Richard N.; Golde, David W.
PATENT ASSIGNEE(S): Sloan-Kettering Institute for Cancer Research, USA
SOURCE: PCT Int. Appl., 115 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
WO 9411007	A1	19940526	WO 1993-US10952		19931112	<--
W: AU, CA, JP, US						
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE						
US 5451518	A	19950919	US 1992-976378		19921113	<--
CA 2149046	AA	19940526	CA 1993-2149046		19931112	<--
AU 9456031	A1	19940608	AU 1994-56031		19931112	<--
EP 667780	A1	19950823	EP 1994-901443		19931112	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE						
JP 08506006	T2	19960702	JP 1993-512375		19931112	<--
PRIORITY APPLN. INFO.:			US 1992-976378	A	19921113	<--
			WO 1993-US10952	W	19931112	<--

ED Entered STN: 03 Sep 1994
AB A purified membrane-bound ceramide-activated protein kinase having an apparent mol. weight of about 97 kD as determined by SDS polyacrylamide gel electrophoresis is provided. The protein kinase of the invention functions as a key element in a **sphingomyelin** pathway using ceramide as a second messenger. This protein kinase specifically phosphorylates the threonine residue in a Pro-Leu-Thr-Pro containing polypeptide. Methods of determining whether an agent is capable of specifically

inhibiting or stimulating the phosphorylation activity of the ceramide-activated protein kinase are also provided, as are a method of **treating** a subject having an inflammatory disorder, a method of **treating** a human subject infected with HIV so as to reduce the proliferation of HIV in the human subject, and a method of **treating** a subject having a disorder associated with poor stem-cell growth (e.g. aplastic anemia).

IC ICM A61K033-00
ICS A61K035-55; A61K037-52; A61K045-05; C07K003-00; C12N009-12; C12Q001-48

CC 7-2 (Enzymes)
Section cross-reference(s): 1

ST ceramide activated protein kinase; **sphingomyelin** signal transduction pathway protein kinase; signal transduction ceramide activated protein kinase; antiinflammatory inhibitor ceramide activated protein kinase; HIV inhibitor ceramide activated protein kinase

IT **Sphingosines**
RL: BIOL (Biological study)
(EGF-receptor peptide phosphorylation **stimulation** with, ceramide-activated protein kinase in relation to)

IT Phosphorylation, biological
(by ceramide-activated protein kinase, **sphingomyelin** signal transduction pathway and related **therapeutics** in relation to)

IT Virucides and Virustats
(inhibitors of phosphorylation activity of ceramide-activated protein kinase, for HIV infection **treatment**)

IT Kinetics, **enzymic**
(of **ceramide**-activated protein kinase phosphorylation of EGF-receptor peptide)

IT Ceramides
RL: BIOL (Biological study)
(protein kinase activated by, characterization of, **sphingomyelin** signal transduction pathway and related **therapeutics** in relation to)

IT **Sphingomyelins**
RL: BIOL (Biological study)
(signal transduction pathway, ceramide-activated protein kinase characterization in relation to)

IT Signal transduction, biological
(**sphingomyelin** pathway, ceramide-activated protein kinase characterization in relation to)

IT Lupus erythematosus
(**treatment** of, inhibitors of phosphorylation activity of ceramide-activated protein kinase of helper T-cells and macrophages for)

IT Anemia (disease)
(aplastic, **treatment** of, agents stimulating phosphorylation activity of ceramide-activated protein kinase for)

IT **Transplant and Transplantation**
(graft-vs.-host reaction, **treatment** of, inhibitors of phosphorylation activity of **ceramide**-activated protein kinase of helper T-cells and macrophages for)

IT Virus, animal
(human immunodeficiency, **treatment** of infection with, inhibitors of phosphorylation activity of ceramide-activated protein kinase for)

IT Lymphokines and Cytokines
RL: BIOL (Biological study)
(interleukin 1, phosphorylation activity of ceramide-activated protein kinase stimulation with, for **treatment** of disease associated

with poor stem-cell growth)
IT Shock
(septic, **treatment** of, inhibitors of phosphorylation activity of ceramide-activated protein kinase of helper T-cells and macrophages for)
IT Cell
(stem, **treatment** of disorder associated with poor growth of, agents stimulating phosphorylation activity of ceramide-activated protein kinase for)
IT Intestine, disease
(ulcerative colitis, **treatment** of, inhibitors of phosphorylation activity of ceramide-activated protein kinase of helper T-cells and macrophages for)
IT 9026-43-1, Protein kinase
RL: BIOL (Biological study)
(ceramide-activated, characterization of, **sphingomyelin** signal transduction pathway and related **therapeutics** in relation to)

L161 ANSWER 23 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1992:504103 HCAPLUS
DOCUMENT NUMBER: 117:104103
TITLE: Neuroprotective **effect** of **glycosphingolipids** in in vitro and in vivo models of excitotoxicity
AUTHOR(S): Manev, H.; Guidotti, A.; Costa, E.
CORPORATE SOURCE: Med. Sch., Georgetown Univ., Washington, DC, 20007, USA
SOURCE: Fidia Research Foundation Symposium Series (**1992**), 9(Excitatory Amino Acids), 103-7
CODEN: FRFSEL; ISSN: 1040-0451
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 20 Sep 1992
AB **Glycosphingolipids**, natural gangliosides and, even more potently, their semisynthetic derivs., protect neurons in culture from excitatory amino acid-induced toxicity. They also ameliorate the consequences of stroke in the in vivo animal model, suggesting the receptor abuse-dependent antagonism **pharmacol.** profile of these compds.
CC 1-11 (Pharmacology)
ST **glycosphingolipid** excitatory amino acid neurotoxicity; stroke **glycosphingolipid**
IT Nerve, disease
(excitatory amino acid-**induced**, **glycosphingolipids** **inhibition** of)
IT Cytoprotective agents
(**glycosphingolipids** as, in neurotoxicity from excitatory amino acids)
IT **Glycosphingolipids**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(neuroprotective activity of, against excitatory amino acid-**induced** toxicity, **stroke treatment** in relation to)
IT Amino acids, biological studies
RL: PRP (Properties)
(excitatory, neurotoxicity of, **glycosphingolipids** **antagonism** of)
IT **Brain, disease**

(**stroke, glycosphingolipids treatment** of, excitatory amino acid **antagonism** in relation to)

L161 ANSWER 24 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1990:116707 HCAPLUS
DOCUMENT NUMBER: 112:116707
TITLE: Metabolism of exogenous galactosylceramide in the twitcher mouse brain
AUTHOR(S): Mitsuo, Kunihiko; Kobayashi, Takuro; Shinnoh, Nobue; Goto, Ikuo
CORPORATE SOURCE: Fac. Med., Kyushu Univ., Fukuoka, 812, Japan
SOURCE: Neurochemical Research (**1989**), 14(12), 1191-4
CODEN: NEREDZ; ISSN: 0364-3190
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 31 Mar 1990
AB The in vivo metabolism of galactosylceramide (gal-cer) in normal mice and in twitcher mice, a model of human Krabbe's disease, was examined following intracerebral **administration** of gel-cer containing [L-14C]stearic acid. In normal mice, gal-cer was hydrolyzed to ceramide within 6 h and ceramide was hydrolyzed to **sphingosine** and fatty acid. Most of the released fatty acid was immediately incorporated into other lipids. About 75% of injected gal-cer was hydrolyzed 80 h after the injection, while in the twitcher mouse, only 17% of gal-cer was hydrolyzed. There was no evidence of any accumulation of gal-cer in the brain. This discrepancy may be due to the different sorting routes of biosynthesized and exogenously-**administered** gal-cer in the mouse brain. Most of the biosynthesized gal-cer is incorporated into myelin, while the injected gal-cer is incorporated into lysosomes.
CC 14-10 (Mammalian Pathological Biochemistry)
IT **Brain, disease or disorder**
(Krabbe's, **galactosylceramide** metabolism by brain in twitcher mouse model of)
IT **85305-88-0**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabolism of, by **brain** of twitcher mouse)
IT **85305-88-0**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabolism of, by **brain** of twitcher mouse)
RN 85305-88-0 HCAPLUS
CN Ceramide, 1-O-β-D-galactopyranosyl- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L161 ANSWER 25 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1989:5762 HCAPLUS
DOCUMENT NUMBER: 110:5762
TITLE: **Lysosphingolipids** and mitochondrial function. II. Deleterious **effects** of **sphingosylphosphorylcholine**
AUTHOR(S): Strasberg, Paula M.; Callahan, John W.
CORPORATE SOURCE: Res. Inst., Hosp. Sick Child., Toronto, ON, M5G 1X8, Can.
SOURCE: Biochemistry and Cell Biology (**1988**), 66(12), 1322-32
CODEN: BCBIEQ; ISSN: 0829-8211
DOCUMENT TYPE: Journal

LANGUAGE: English
ED Entered STN: 06 Jan 1989
AB Psychosine, **sphingosylphosphorylcholine** (52-104 μM), and other **glycosphingolipids stimulate** mitochondrial respiration (up to 500%) and **inhibit** oxidative phosphorylation to varying degrees. Above 104 μM, these functions as well as uptake of Ca2+ are **prevented.** At 104 μM, **sphingosylphosphorylcholine inhibits** the mitochondrial ATPase reaction in submitochondrial particles by 48%. Both **sphingosylphosphorylcholine** and psychosine **enhance** the active phosphate-dependent swelling of mitochondria. Passive swelling occurs in the presence of rotenone (when swelling does not normally occur) and under hypotonic conditions. A direct interaction of **sphingosylphosphorylcholine** with membranes is demonstrated by a discharge of the proton gradient across mitochondrial membranes, hemolysis of red blood cells, and binding to inner and outer mitochondrial membranes. Thus, lysoshingolipids bind strongly to mitochondrial membranes and markedly alter mitochondrial function. This alteration would affect the ATP levels, thereby altering a wide range of ATP-dependent cellular functions. These results offer a partial explanation for the pathogenesis of representative lysosomal storage diseases (Neimann-Pick variants, Gaucher's disease, Krabbe's disease).
CC 14-14 (Mammalian Pathological Biochemistry)
ST **lysosphingolipid** mitochondria function lysosomal storage disease; **sphingosylphosphorylcholine** mitochondria function lysosomal storage disease
IT Animal respiration
(by mitochondria, **sphingosylphosphorylcholine** and other **lysosphingolipids effects** on, lysosomal storage diseases in relation to, in humans and laboratory animals)
IT Hemolysis
(from **sphingosylphosphorylcholine** and other **lysosphingolipids**)
IT Mitochondria
(function and morphol. of, **sphingosylphosphorylcholine** and other **lysosphingolipids effects** on, lysosomal storage diseases in relation to, in humans and laboratory animals)
IT **Glycosphingolipids**
RL: BIOL (Biological study)
(mitochondria function and morphol. responses to, lysosomal storage diseases in relation to, in humans and laboratory animals)
IT Swelling, biological
(of mitochondria, from **sphingosylphosphorylcholine** and other **lysosphingolipids**, lysosomal storage diseases in relation to, in humans and laboratory animals)
IT Gaucher's disease
Niemann-Pick disease
(pathogenesis of, **sphingosylphosphorylcholine** and other **lysosphingolipids effects** on mitochondrial function and morphol. in relation to, in humans and laboratory animals)
IT **Brain, disease or disorder**
(Krabbe's, pathogenesis of, **sphingosylphosphorylcholine** and other **lysosphingolipids effects** on mitochondrial function and morphol. in relation to, in humans and laboratory animals)
IT Lysosome
(disease, storage, pathogenesis of, **sphingosylphosphorylcholine** and other **lysosphingolipids effects** on mitochondrial function and morphol. in relation to, in humans and laboratory animals)
IT Animal metabolism

(disorder, lysosomal storage, pathogenesis of, **sphingosylphosphorylcholine** and other **lysosphingolipids effects** on mitochondrial function and morphol. in relation to, in humans and laboratory animals)

IT **Sphingolipids**
RL: BIOL (Biological study)
(lyso-, mitochondria function and morphol. responses to, lysosomal storage diseases in relation to, in humans and laboratory animals)

IT Phosphorylation, biological
(oxidative, by mitochondria, **sphingosylphosphorylcholine** and other **lysosphingolipids effects** on, lysosomal storage diseases in relation to, in humans and laboratory animals)

IT 56-65-5, 5'-ATP, biological studies 58-64-0, 5'-ADP, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabolism of, by mitochondria, **lysosphingolipids effects** on, lysosomal storage diseases in relation to, in humans and laboratory animals)

IT 107-73-3D, **sphingosyl** derivative 2238-90-6, Psychosine
85305-87-9, Glucocerebroside
RL: BIOL (Biological study)
(mitochondria function and morphol. responses to, lysosomal storage diseases in relation to, in humans and laboratory animals)

IT 9000-83-3, ATPase
RL: BIOL (Biological study)
(of mitochondria, **sphingosylphosphorylcholine** and other **lysosphingolipids effects** on, lysosomal storage diseases in relation to, in humans and laboratory animals)

IT 7440-70-2, Calcium, biological studies 12408-02-5, biological studies
RL: BIOL (Biological study)
(transport of, by mitochondria, **lysosphingolipids effects** on, lysosomal storage diseases in relation to, in humans and laboratory animals)

IT **85305-87-9, Glucocerebroside**
RL: BIOL (Biological study)
(mitochondria function and morphol. responses to, lysosomal storage diseases in relation to, in humans and laboratory animals)

RN 85305-87-9 HCAPLUS
CN Ceramide, 1-O-β-D-glucopyranosyl- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L161 ANSWER 26 OF 127 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1986:440521 HCAPLUS
DOCUMENT NUMBER: 105:40521
TITLE: Cerebrosides and psychosine disrupt mitochondrial functions
AUTHOR(S): Strasberg, Paula
CORPORATE SOURCE: Res. Inst., Hosp. Sick Child., Toronto, ON, M5G 1X8, Can.
SOURCE: Biochemistry and Cell Biology (**1986**), 64(5), 485-9
CODEN: BCBIEQ; ISSN: 0829-8211
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 09 Aug 1986
AB Glucocerebroside and galactocerebroside increased the respiratory rate of rat liver and rabbit brain mitochondria by 33-400% and produced an average 30% decrease in oxidative phosphorylation. Psychosine stimulated mitochondrial respiration 66-700%. At concns. over 100 μg/mg

mitochondrial protein, oxidative phosphorylation was completely inhibited. Atractyloside did not **prevent** the respiratory stimulation. Ca2+ transport was blocked and addition of ATP could not overcome this inhibition. The possible deleterious **effect** of **glycosphingolipids** on the conformation of the mitochondrial membrane and cellular bioenergetics is discussed in relation to the toxicity of accumulating **glycosphingolipids** in Gaucher and Krabbe diseases.

CC 14-15 (Mammalian Pathological Biochemistry)

IT **Glycosphingolipids**
RL: BIOL (Biological study)
(accumulation of, in Gaucher and Krabbe diseases, **cerebroside** and psychosine **effect** on mitochondrial metabolism in relation to)

IT Gaucher's disease
(**glycosphingolipid** accumulation in, cerebrosides and psychosine **effects** on mitochondrial metabolism in relation to)

IT **Sphingosines**
RL: BIOL (Biological study)
(mitochondria metabolism response to, Gaucher and Krabbe diseases in relation to)

IT **Brain, disease or disorder**
(Krabbe's, **glycosphingolipid** accumulation in, **cerebrosides** and psychosine **effects** on mitochondrial metabolism in relation to)

IT 2238-90-6 85305-87-9 **85305-88-0**
RL: BIOL (Biological study)
(mitochondria metabolism response to, Gaucher and Krabbe diseases in relation to)

IT **85305-88-0**
RL: BIOL (Biological study)
(mitochondria metabolism response to, Gaucher and Krabbe diseases in relation to)

RN 85305-88-0 HCAPLUS

CN Ceramide, 1-O-β-D-galactopyranosyl- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d iall abeq tech abex 27-47
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, PASCAL, LIFESCI, BIOENG, BIOTECHDS, DRUGU, SCISEARCH' - CONTINUE? (Y)/N:y

L161 ANSWER 27 OF 127 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN DUPLICATE 3
ACCESSION NUMBER: 2002-503705 [54] WPIX
DOC. NO. CPI: C2002-143303
TITLE: New compound F-16053A useful as a pharmaceutical is collected from a fermentation culture of Stereum ochraceoflavum SANK 19400.
DERWENT CLASS: B05 D16
PATENT ASSIGNEE(S): (SANY) SANKYO CO LTD
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
JP 2002114741	A	20020416	(200254)*		12	C07C069-28

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE	
JP 2002114741	A	JP 2000-310561	20001011	<--

PRIORITY APPLN. INFO: **JP 2000-310561**
20001011
INT. PATENT CLASSIF.:
MAIN: C07C069-28
SECONDARY: A61K031-23; **A61P003-10**; **A61P007-02**; **A61P009-10**; **A61P029-00**; **A61P035-00**; **A61P035-04**; **A61P037-06**; **A61P037-08**; C07C069-013; C07C069-03; C12N001-14; C12P007-64
ADDITIONAL: **C12N009-99**
INDEX: C12R001:645; C12R001:645; C12P007-64; C12N001-14
BASIC ABSTRACT:
JP2002114741 A UPAB: 20020823
NOVELTY - Compound F-16053A (I) useful as a pharmaceutical collected from a fermentation culture of Stereum ochraceoflavum SANK 19400, is new.
DETAILED DESCRIPTION - Compound F-16053A (I) useful as a pharmaceutical collected from a fermentation culture of Stereum ochraceoflavum SANK 19400, is new.
ACTIVITY - Antiarteriosclerotic; Antidiabetic; Anticoagulant; Thrombolytic; Antiinflammatory; Immunomodulator; Cytostatic; Antiallergic; Vasotropic.
No suitable data given.
MECHANISM OF ACTION - None given.
USE - (I) is useful for prevention/treatment of **arteriosclerosis**, diabetes, thrombosis, inflammation, immunological disorders, cancer, its metastasis, allergy, and **restenosis** after percutaneous transluminal **coronary** angioplasty (PTCA) (claimed).
ADVANTAGE - The agent possesses potent **sphingosine** kinase **inhibitory** activity.
Dwg.0/0
FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B04-F09; B10-G02; B11-C08E1; B14-C03; **B14-F01G**; **B14-F04**; **B14-F07**; B14-G02A; B14-G03; B14-H01; B14-S04; D05-A04; D05-C
ABEX UPTX: 20020823
ADMINISTRATION - None given.
No dosage given.

EXAMPLE - Stereum ochraceoflavum SANK 19400 (FERM BP-7244) was aseptically cultured at 23 degrees C and 210 revolutions per minute (rpm) for 7 days on a medium (each 80 ml) of maltose, glucose, polypeptone, yeast extract, and minerals. The culture (1.2 L) thus obtained was centrifuged and the separated cells were extracted with 80% aqueous acetone (1 L) for 3 hours at room temperature. After filtration, the filtrate was concentrated and the residual aqueous part (0.5 L) was made pH 3. This was extracted with EtOAc (3x0.5 L) to give, after evaporation in vacuo, an oil (4.3 g). This was chromatographed on Daiaion HP-20, Cosmocil 140-OPN, and Senshu Pak PEGASIL ODS in aqueous acetonitrile to give, after lyophilization, F-16053A (120 mg).

L161 ANSWER 28 OF 127 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN DUPLICATE 4
ACCESSION NUMBER: 2001-514770 [56] WPIX

DOC. NO. NON-CPI: N2001-381284
DOC. NO. CPI: C2001-153907
TITLE: An isolated **Sphingosine** kinase polypeptide useful for treating a SphK-associated disorder especially cancer, **restenosis** or **ischemia** in a human.
DERWENT CLASS: B04 D16 P14 S03
INVENTOR(S): GERRITSEN, M E; RASTELLI, L; RASTELLI, L K
PATENT ASSIGNEE(S): (CURA-N) CURAGEN CORP; (GETH) GENENTECH INC; (GERR-I) GERRITSEN M E; (RAST-I) RASTELLI L
COUNTRY COUNT: 95
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2001060990	A2	20010823	(200156)*	EN	117	C12N009-12<--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW						
AU 2001038283	A	20010827	(200176)			C12N009-12<--
US 2002082203	A1	20020627	(200245)			G01N033-00
EP 1257637	A2	20021120	(200301)	EN		C12N009-12<--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR						
US 6858427	B2	20050222	(200515)			C12N015-52
AU 2001238283	B2	20050512	(200535)			C12N009-12<--
US 2005123942	A1	20050609	(200538)			A61K048-00
AU 2005203590	A1	20050901	(200565)#			C12N009-12<--
AU 2001238283	B8	20050512	(200568)			C12N009-12<--

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE	
WO 2001060990	A2		WO 2001-US4789	20010214	
AU 2001038283	A		AU 2001-38283	20010214	
US 2002082203	A1	Provisional	US 2000-182360P	20000214	<--
		Provisional	US 2000-191261P	20000322	<--
			US 2001-784810	20010214	
EP 1257637	A2		EP 2001-910701	20010214	
			WO 2001-US4789	20010214	
US 6858427	B2	Provisional	US 2000-182360P	20000214	<--
		Provisional	US 2000-191261P	20000322	<--
			US 2001-784810	20010214	
AU 2001238283	B2		AU 2001-238283	20010214	
US 2005123942	A1	Provisional	US 2000-182360P	20000214	<--
		Provisional	US 2000-191261P	20000322	<--
		Div ex	US 2001-784810	20010214	
			US 2004-876281	20040624	
AU 2005203590	A1	Div ex	AU 2001-238283	20010214	
			AU 2005-203590	20050811	
AU 2001238283	B8		AU 2001-238283	20010214	

FILING DETAILS:

PATENT NO	KIND	PATENT NO

AU 2001038283	A	Based on	WO 2001060990
EP 1257637	A2	Based on	WO 2001060990
AU 2001238283	B2	Previous Publ.	AU 2001238283
		Based on	WO 2001060990
US 2005123942	A1	Div ex	US 6858427
AU 2001238283	B8	Previous Publ.	AU 2001238283
		Based on	WO 2001060990

PRIORITY APPLN. INFO: **US 2000-191261P 20000322; US 2000-182360P 20000214;** US 2001-784810 20010214; US 2004-876281 20040624; AU 2005-203590 20050811

INT. PATENT CLASSIF.:
MAIN: A61K048-00; **C12N009-12**; C12N015-52; G01N033-00
SECONDARY: A01K067-00; A61K038-45; A61K039-395; **A61P009-10**; **A61P035-00**; C07H021-04; C07K016-40; C12N005-06; C12N015-11; C12N015-54; C12N015-63; C12P021-02; C12Q001-68; G01N033-53

BASIC ABSTRACT:

WO 200160990 A UPAB: 20011001

NOVELTY - An isolated polypeptide (I) comprising a 384 or 471 amino acid sequence fully defined in the specification, their variants, fragments or naturally occurring variants, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) An isolated nucleic acid molecule (II) encoding (I), encoding the complement, is a naturally occurring allelic nucleic acid variant or comprising a 1600 or 1840 fully defined base pair sequence given in the specification or a nucleic acid molecule that hybridizes under stringent conditions to the defined sequences;

(2) A vector (III) comprising (II);

(3) A cell (IV) comprising (III);

(4) An antibody (V) that binds immunospecifically to (I);

(5) Determining (M1) the presence or amount of (I) in a sample comprising introducing the sample to (V) and determining the presence or amount of bound (V);

(6) Determining (M2) the presence or amount of (II) in a sample comprising introducing the sample to a probe that binds to (II) and determining the presence or amount of bound probe in the sample;

(7) Identifying (M3) an agent that binds to (I) comprising contacting (I) with the agent and determining whether the agent binds to (I);

(8) Identifying (M4) an agent that modulates the expression or activity of (I) comprising contacting a cell expressing (I) with the agent and determining whether the agent modulates expression or activity of (I);

(9) Modulating (M5) the activity of (I) comprising introducing a cell sample expressing (I) with a compound that binds to (I);

(10) A kit comprising a pharmaceutical composition of (I), (II) or (V);

(11) Determining (M6) the presence of or predisposition to a disease associated with altered levels of (I) or (II) in a first mammalian subject comprising:

(a) measuring the level of expression of (I) or (II) in a sample from the first mammalian subject; and

(b) comparing the amount of (I) or (II) in the sample to the amount of (I) or (II) in a control sample from a second mammalian subject known not to have the disease where an alteration in expression level of (I) or (II) in the first mammalian subject indicates presence of or predisposition to the disease;

(12) A non-human transgenic animal (VI) comprising (II);
(13) Identifying (M7) an agent that modulates the expression or activity of (I) comprising contacting (VI) with the agent and determining whether the agent modulates expression or activity of the polypeptide.
ACTIVITY - Cytostatic; vasotropic.
MECHANISM OF ACTION - **Sphingosine** kinase; **sphingosine** kinase **inhibitor**; gene therapy; antisense-therapy.
No supporting data is given.
USE - (I), (II) and (V) are useful for treating a SphK-associated disorder especially cancer, **restenosis** or **ischemia** in a human. M1 is useful for determining the presence or amount of (I) in a sample. M2 is useful for determining the presence or amount of (II) in a sample. M3 is useful for identifying an agent that binds to (I). M4 is useful for identifying an agent that modulates the expression or activity of (I). M5 is useful for modulating the activity of (I). M6 is useful for determining the presence of or predisposition to a disease associated with altered levels of (I) or (II). M7 is useful for Identifying (M7) an agent that modulates the expression or activity of (I) (all claimed).
Dwg.0/5

FILE SEGMENT: CPI EPI GMPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B04-C01G; B04-E03E; B04-E05; B04-E06; B04-E08; B04-F0100E; B04-G03; B04-G21; B04-L04; B04-P0100E; B11-C08E; B11-C08E5; B12-K04A; B12-K04E; B12-K04F; **B14-F02**; B14-H01; B14-S03; D05-H09; D05-H11A; D05-H12A; D05-H12D1; D05-H12D2; D05-H12E; D05-H14; D05-H16A; D05-H17A3
EPI: S03-E14H4
TECH UPTX: 20011001
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Polypeptide: Variants of (I) are by of a single nucleotide polymorphism of (II) or where an amino acid is changed to provide a conservative substitution.
Preferred Vector: (III) further comprises a promoter operably linked to (II).
Preferred Antibody: (V) is a monoclonal and/or humanized antibody.
Preferred Method: In M2, the presence or amount of (II) is used as a marker for cell or tissue type preferably cancerous tissue. In M3, the agent is a cellular receptor or downstream effector. In M6, the predisposition is to cancers.
Preferred Transgenic Animal: (VI) comprises a transgene **disrupting** an endogenous **sphingosine** kinase gene.
Preparation: (I) is prepared by standard recombinant techniques.
ABEX UPTX: 20011001
ADMINISTRATION - (I), (II) and (V) are administered by catheter, **stent** or syringe. Examples of routes of administration include intravenous, intradermal, oral or rectal. Common dosage ranges from 0.1mg/kg body weight to about 50 mg/kg body weight.

EXAMPLE - No suitable example is given.

L161 ANSWER 29 OF 127 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-663394 [62] WPIX
CROSS REFERENCE: 1999-263700 [22]; 2003-605464 [57]
DOC. NO. CPI: C2003-180196
TITLE: Identifying an agent that **modulates** **sphingolipid** metabolism for treating e.g., breast cancer by culturing a homozygous null mutant Drosophila melanogaster in the absence and presence of a candidate agent.

DERWENT CLASS: B04 D16 P14
INVENTOR(S): FYRST, H; SABA, J D
PATENT ASSIGNEE(S): (CHIL-N) CHILDREN'S HOSPITAL & RES CENT AT OAKLAND; (CHIL-N) CHILDRENS HOSPITAL & RES CENT AT OAKLAND; (CHIL-N) CHILDREN'S HOSPITAL OAKLAND RES INST; (CHIL-N) CHILDREN'S HOSPITAL & RES INST AT OAKLAND
COUNTRY COUNT: 103
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2003062390	A2	20030731	(200362)*	EN	93	C12N000-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW						
US 2003175939	A1	20030918	(200362)			C12N009-88<--
US 2003219782	A1	20031127	(200378)			C12Q001-68
AU 2003216076	A1	20030902	(200422)			C12N000-00
US 2004126834	A1	20040701	(200444)			C12Q001-44
US 6830881	B2	20041214	(200501)			C12N009-88<--
EP 1517989	A2	20050330	(200522)	EN		C12N009-12<--
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR						
JP 2005531285	W	20051020	(200569)		117	C12Q001-42
AU 2003216076	A8	20051110	(200634)			C12N009-12<--

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE	
WO 2003062390	A2		WO 2003-US1739	20030117	
US 2003175939	A1	CIP of	US 1997-939309	19970929	<--
		CIP of	US 1999-356643	19990719	<--
			US 2002-53510	20020117	
US 2003219782	A1	Provisional	US 2002-349582P	20020117	
			US 2003-348052	20030117	
AU 2003216076	A1		AU 2003-216076	20030117	
US 2004126834	A1	CIP of	US 2002-53510	20020117	
		Provisional	US 2002-349582P	20020117	
		CIP of	US 2003-348052	20030117	
			US 2003-622011	20030716	
US 6830881	B2	CIP of	US 1997-939309	19970929	<--
		CIP of	US 1999-356643	19990719	<--
			US 2002-53510	20020117	
EP 1517989	A2		EP 2003-732010	20030117	
			WO 2003-US1739	20030117	
JP 2005531285	W		JP 2003-562258	20030117	
			WO 2003-US1739	20030117	
AU 2003216076	A8		AU 2003-216076	20030117	

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 2003175939	A1	CIP of	US 6423527
		CIP of	US 6569666

AU 2003216076	A1	Based on	WO 2003062390
US 6830881	B2	CIP of	US 6423527
		CIP of	US 6569666
EP 1517989	A2	Based on	WO 2003062390
JP 2005531285	W	Based on	WO 2003062390
AU 2003216076	A8	Based on	WO 2003062390

PRIORITY APPLN. INFO: US 2002-349582P 20020117; US 2002-53510 20020117; **US 1997-939309 19970929; US 1999-356643 19990719;** US 2003-348052 20030117; US 2003-622011 20030716

INT. PATENT CLASSIF.:

MAIN: C12N000-00; **C12N009-12**; **C12N009-88**; C12Q001-42; C12Q001-44; C12Q001-68

SECONDARY: A01K067-00; A01K067-33; A61K031-137; A61K031-7088; A61K038-00; A61K039-395; A61K045-00; A61K048-00; A61K049-00; **A61P001-04**; **A61P011-00**; **A61P013-12**; **A61P015-00**; **A61P025-00**; **A61P035-00**; **A61P035-04**; **A61P043-00**; C07H021-04; C07K017-00; C12N001-18; C12N005-00; C12N005-06; C12N015-00; C12N015-09; C12P021-02; C12P021-06; C12Q001-34; C12Q001-48; G01N033-00; G01N033-15; G01N033-50

BASIC ABSTRACT:

WO2003062390 A UPAB: 20060526

NOVELTY - Identifying an agent that **modulates** **sphingolipid** metabolism, is new.

DETAILED DESCRIPTION - Identifying an agent that **modulates** **sphingolipid** metabolism comprises:

(a) culturing a homozygous null mutant Drosophila melanogaster in the absence and presence of a candidate agent under conditions and for a time sufficient to observe in the mutant Drosophila melanogaster an effect of the agent on a level of either at least one **sphingolipid** intermediate or activity of at least one component of a **sphingolipid** pathway, where the mutant Drosophila melanogaster comprises a P-element transposon insertion in a gene encoding a component of a **sphingolipid** pathway that results in at least one of an **altered** level of at least one **sphingolipid** intermediate and an **altered** activity level of at least one **sphingolipid** pathway component; and

(b) comparing the level of either the **sphingolipid** intermediate that is generated or the activity of the **sphingolipid** pathway component, in the presence of the candidate agent to the level in the absence of the candidate agent, where an **altered** level indicates the agent **modulates** **sphingolipid** metabolism.

INDEPENDENT CLAIMS are also included for the following:

(1) identifying an agent that **modulates** **sphingolipid** signaling;

(2) a composition;

(3) preparing a **sphingosine**-1-phosphate lyase (SPL) polypeptide;

(4) identifying an agent that modulates SPL activity;

(5) identifying an agent that modulates SPL activity;

(6) inhibiting growth of a cancer cell;

(7) inhibiting development and/or metastasis of cancer in a mammal;

(8) determining the presence of cancer in a patient;

(9) diagnosing a disease associated with **altered** **sphingolipid** metabolism;
(10) determining the presence of a cancer in a patient; and
(11) treating a disease associated with **altered** **sphingolipid** metabolism in a patient.
ACTIVITY - Cytostatic. No biological data given.
MECHANISM OF ACTION - Gene therapy.
USE - The method is useful for identifying an agent that **modulates** **sphingolipid** metabolism for preparing a composition for treating a disease associated with **altered** **sphingolipid** metabolism in a patient, e.g., colon cancer, breast cancer, uterine cancer, stomach cancer, ovarian cancer, lung cancer, kidney cancer, adenocarcinoma of the rectum or hereditary sensory neuropathy type 1 or any one of the **sphingolipidoses** (claimed).
Dwg.0/3

FILE SEGMENT: CPI GMPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B04-B01B; B04-B03C; B04-E01; B04-G03; B04-G05; B04-L04; B04-L06; B04-L0600E; B04-P01C0E; B05-B01P; B10-B03B; B11-C08E2; B11-C08E3; B11-C08E5; B12-K04A1; B12-K04E; B12-K04F; B14-D06; B14-D08; B14-H01; D05-C03E; D05-H09; D05-H17A3

TECH UPTX: 20030928
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: Identifying an agent that **modulates** **sphingolipid** metabolism comprises:
(a) culturing a homozygous null mutant Drosophila melanogaster in the absence and presence of a candidate agent under conditions and for a time sufficient to observe in the mutant Drosophila melanogaster an effect of the agent on a level of either at least one **sphingolipid** intermediate or activity of at least one component of a **sphingolipid** pathway, where the mutant Drosophila melanogaster comprises a P-element transposon insertion in a gene encoding a component of a **sphingolipid** pathway that results in an **altered** activity level of at least one **sphingolipid** pathway component, and where the mutant Drosophila melanogaster exhibits a flightless phenotype that results from the insertion; and
(b) comparing the flight performance of the mutant Drosophila that is cultured in the presence of the candidate agent to the flight performance in the absence of the candidate agent, where an increased flight performance of the mutant Drosophila melanogaster indicates that the agent **modulates** **sphingolipid** metabolism.
The **altered** level of a **sphingolipid** intermediate comprises an increase in C14/16 phosphorylated long chain bases. The gene encoding a component of a **sphingolipid** pathway comprises a polynucleotide sequence comprising 1638, 2629 or 2609 bp. The homozygous null mutant Drosophila melanogaster comprises a tumor. It comprises a T2 segment that comprises abnormal developmental patterning of thoracic muscles. The **altered** level of the **sphingolipid** intermediate that is generated in the presence of the candidate agent comprises a decrease or an increase in **sphingosine**-1-phosphate.
The **altered** level of the activity of the **sphingolipid** pathway component in the presence of the candidate agent comprises a decrease or an increase in SPL activity. The **altered** level of the activity of the **sphingolipid** pathway component in the presence of the candidate agent comprises a decrease or an increase in **sphingosine** kinase (SK) activity. The agent **inhibits** SK or SPL activity. The agent comprises a 1-aryl-2-dimethylaminopropane-1, 3-diol derivative. The derivative comprises a substitution of a fatty acid amide group or of two N-methyl groups. The agent increases activity of serine **palmitoyltransferase**. The **altered** level of the

sphingolipid intermediate that is generated in the presence of the candidate agent comprises a decrease or an increase in **sphingosine** -1-phosphate. The **altered** level of the activity of the **sphingolipid** pathway component in the presence of the candidate agent comprises a decrease or an increase in SPL activity. The **altered** level of the activity of the **sphingolipid** pathway component in the presence of the candidate agent comprises a decrease or an increase in SK activity. Identifying an agent that **modulates sphingolipid** signaling comprises:
(a) culturing a homozygous null mutant Drosophila melanogaster in the absence and presence of a candidate agent under conditions and for a time sufficient to observe in the mutant Drosophila melanogaster an effect of the agent on a level of either at least one **sphingolipid** intermediate or activity of at least one component of a **sphingolipid** pathway, where the mutant Drosophila melanogaster comprises a P-element transposon insertion in a gene encoding a component of a **sphingolipid** pathway that results in at least one of an **altered** level of at least one **sphingolipid** intermediate and an **altered** activity level of at least one **sphingolipid** pathway component; and
(b) comparing the level of either the **sphingolipid** intermediate that is generated or the activity of the **sphingolipid** pathway component, in the presence of the candidate agent to the level in the absence of the candidate agent, where an **altered** level indicates the agent **modulates sphingolipid** signaling.
Identifying an agent that **modulates** SPL activity comprises:
(a) contacting a candidate agent with an isolated polypeptide that comprises a sequence having 545 amino acids or a sequence having at least 90% identity to the 545-amino acid sequence, where the polypeptide has **sphingosine**-1-phosphate lyase activity, and where the step of contacting is carried out under conditions and for a time sufficient to allow the candidate agent to interact with the polypeptide; and
(b) determining degradation by the polypeptide of **sphingosine** -1-phosphate or its derivative in the presence of the candidate agent, relative to degradation by the polypeptide of **sphingosine** -1-phosphate or its derivative in the absence of the candidate agent.
Identifying an agent that modulates SPL activity comprises:
(a) contacting a candidate agent with a biological sample that comprises a cell which expresses the polypeptide that comprises a sequence having 545 amino acids or a sequence having at least 90% identity to the 545-amino acid sequence, where the polypeptide has SPL activity, and where the step of contacting is carried out under conditions and for a time sufficient to allow the candidate agent to interact with the polypeptide; and
(b) determining degradation by the polypeptide of **sphingosine** -1-phosphate or its derivative in the presence of the candidate agent, relative to degradation by the polypeptide of **sphingosine** -1-phosphate or its derivative in the absence of the candidate agent.

Inhibiting growth of a cancer cell comprises contacting the cancer cell with an agent that increases SPL activity of the polypeptide. The agent increases expression of an endogenous SPL gene. The cancer cell is a breast cancer cell. Inhibiting development and/or metastasis of cancer in a mammal comprises administering to the mammal an agent that increases SPL activity of the polypeptide. The agent is linked to a targeting component, which is an anti-tumor antibody. It binds to an estrogen receptor. The mammal is afflicted with breast cancer.
Determining the presence of cancer in a patient comprises:
(a) contacting a first biological sample comprising at least one polynucleotide and being obtained from a patient suspected of having cancer with at least one oligonucleotide that is specific for a polynucleotide, comprising a sequence having 1707 bp;

(b) detecting an amount of the oligonucleotide that hybridizes to the polynucleotide in the first sample; and
(c) comparing the amount of oligonucleotide that hybridizes to the polynucleotide in the first sample to an amount of oligonucleotide that hybridizes to a polynucleotide in a second biological sample obtained from a normal control subject known to be free of cancer, where a statistically significant decrease in the amount of oligonucleotide that hybridizes to the polynucleotide in the first biological sample relative to the amount of oligonucleotide that hybridizes to the polynucleotide in the second sample signifies the presence of a cancer in the patient.
Diagnosing a disease associated with **altered sphingolipid** metabolism comprises:
(a) contacting a first biological sample comprising at least one polynucleotide and being obtained from a patient suspected of having a disease associated with **altered sphingolipid** metabolism with at least one oligonucleotide that is specific for the polynucleotide;
(b) detecting an amount of the oligonucleotide that hybridizes to the polynucleotide in the first sample; and
(c) comparing the amount of oligonucleotide that hybridizes to the polynucleotide in the first sample to an amount of oligonucleotide that hybridizes to a polynucleotide in a second biological sample obtained from a normal **control** subject known to be free of a disease associated with **altered sphingolipid** metabolism, where a statistically significant decrease in the amount of oligonucleotide that hybridizes to the polynucleotide in the first biological sample relative to the amount of oligonucleotide that hybridizes to the polynucleotide in the second sample signifies the presence of a disease associated with **altered sphingolipid** metabolism in the patient.
Determining the presence of a cancer in a patient comprises:
(a) contacting a first biological sample comprising at least one polynucleotide and being obtained from a patient suspected of having a disease associated with **altered sphingolipid** metabolism with at least one oligonucleotide that is specific for the polynucleotide;
(b) detecting an amount of the oligonucleotide that hybridizes to the polynucleotide in the first sample; and
(c) comparing the amount of oligonucleotide that hybridizes to the polynucleotide in the first sample to an amount of oligonucleotide that hybridizes to a polynucleotide in a second biological sample obtained from a normal **control** subject known to be free of a disease associated with **altered sphingolipid** metabolism, where a statistically significant decrease in the amount of oligonucleotide that hybridizes to the polynucleotide in the first biological sample relative to the amount of oligonucleotide that hybridizes to the polynucleotide in the second sample signifies the presence of a cancer in the patient.
Treating a disease associated with **altered sphingolipid** metabolism in a patient comprises administering the agent to the patient. The disease comprises colon cancer, breast cancer, uterine cancer, stomach cancer, ovarian cancer, lung cancer, kidney cancer, adenocarcinoma of the rectum, hereditary sensory neuropathy type 1 or any one of the **sphingolipidoses.**
Production (claimed): Preparing a SPL polypeptide comprises:
(a) culturing a host cell transformed or transfected with a nucleic acid construct comprising a promoter operably linked to a polynucleotide comprising the 1638-bp sequence; and
(b) recovering a **sphingosine**-1phosphate lyase polypeptide.
Preferred Composition: The composition comprises:
(a) the agent that increases flight performance in a homozygous null mutant Drosophila melanogaster and an excipient;

(b) the agent that modulates SPL activity of the polypeptide and a carrier;
(c) the polynucleotide; or
(d) an antibody or an antigen-binding fragment that specifically binds a SPL polypeptide, where the antibody increases the ability of the SPL polypeptide to degrade **sphingosine**-1-phosphate.

ABEX UPTX: 20030928
ADMINISTRATION - The composition is administered via oral or parenteral route. No dosage details given.

L161 ANSWER 30 OF 127 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-340094 [37] WPIX
DOC. NO. CPI: C2002-097796
TITLE: New reagent for **modulating** the activity of **sphingosine** kinase-like protein polypeptide or polynucleotide and treating cancer, asthma, allergy, an autoimmune disease, or a central or peripheral nervous system disorder.
DERWENT CLASS: B04 D16
INVENTOR(S): ENCINAS, J; KOSSIDA, S; TAKAO, E
PATENT ASSIGNEE(S): (FARB) BAYER AG; (ENCI-I) ENCINAS J; (KOSS-I) KOSSIDA S
COUNTRY COUNT: 98
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2002028906	A2	20020411	(200237)*	EN	124	C07K017-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW						
AU 2002023593	A	20020415	(200254)			C07K017-00
						C07H021-02
US 2003125533	A1	20030703	(200345)			C12N015-54
EP 1326986	A2	20030716	(200347)	EN		
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR						
JP 2004510429	W	20040408	(200425)		181	C12N015-09
US 2004192580	A1	20040930	(200465)			A61K038-17
AU 2002223593	A8	20051006	(200612)			C12N015-54

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE	
WO 2002028906	A2		WO 2001-EP11516	20011005	
AU 2002023593	A		AU 2002-23593	20011005	
US 2003125533	A1	Provisional	US 2000-238005P	20001006	<--
		Provisional	US 2001-314113P	20010823	
			US 2001-969896	20011004	
EP 1326986	A2		EP 2001-986303	20011005	
			WO 2001-EP11516	20011005	
JP 2004510429	W		WO 2001-EP11516	20011005	
			JP 2002-532488	20011005	
US 2004192580	A1	Provisional	US 2000-238005P	20001006	<--
		Provisional	US 2001-314113P	20010823	
		CIP of	US 2001-969896	20011004	
			US 2003-631958	20031219	
AU 2002223593	A8		AU 2002-223593	20011005	

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002023593	A Based on	WO 2002028906
EP 1326986	A2 Based on	WO 2002028906
JP 2004510429	W Based on	WO 2002028906
AU 2002223593	A8 Based on	WO 2002028906

PRIORITY APPLN. INFO: US 2001-314113P 20010823;
US 2000-238005P
20001006; US 2001-969896
20011004; US 2003-631958
20031219

INT. PATENT CLASSIF.:
MAIN: A61K038-17; C07H021-02; C07K017-00; C12N015-09;
C12N015-54
SECONDARY: A61K031-7088; A61K031-7105; A61K035-76; A61K038-43;
A61K038-55; A61K039-395; A61K045-00; A61K048-00;
A61P011-14; **A61P025-00**;
A61P025-02; **A61P035-00**;
A61P037-06; **A61P037-08**;
A61P043-00; C07H021-04; C12N001-15; C12N001-19;
C12N001-21; C12N005-10; **C12N009-12**; C12N015-62;
C12Q001-02; C12Q001-68; G01N033-15; G01N033-50;
G01N033-53; G01N033-566; G01N033-573

BASIC ABSTRACT:

WO 200228906 A UPAB: 20020626

NOVELTY - A reagent (I) that **modulates** the activity of **sphingosine** kinase-like protein polypeptide or polynucleotide, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated polynucleotide encoding a **sphingosine** kinase-like protein polypeptide that:

(i) comprises or consists of a sequence:

(a) encoding a sequence 50 % identical to a sequence of 326 (S1), 537 (S2), or 562 (S3) amino acids, given in the specification; or

(b) encoding S1, S2, or S3;

(ii) comprises a sequence (S4) of 979 or 4413 base pairs (bp), given in the specification;

(iii) hybridizes under stringent conditions to (i) or (ii);

(iv) deviates from (i) - (iii) due to degeneracy of the genetic code; or

(v) represents a fragment, derivative or allelic variation of (i) - (iv);

(2) an expression vector comprising (1);

(3) a host cell comprising (2);

(4) a purified **sphingosine** kinase-like protein polypeptide encoded by (1);

(5) producing (4) comprising culturing (3) and recovering (4) from the host cell culture;

(6) detecting a polynucleotide encoding (4) in a biological sample, comprising hybridizing (1) to a nucleic acid material of a biological sample, forming a hybridization complex, and detecting the complex;

(7) detecting (1) or (4), comprising contacting a biological sample with a reagent that specifically interacts with (1) or (4);

(8) a diagnostic kit for conducting (6) and (7);

(9) screening for agents that decrease the activity of (4) comprising

contacting a test compound with (4) or (1) and detecting binding, where the test compound that binds to (4) or (1) is identified as a potential therapeutic agent for decreasing the activity of (4);

(10) screening for agents that regulate the activity of (4) comprising contacting a test compound with (4), and detecting the activity of (4), where an increase or decrease in activity identifies a potential therapeutic agent for increasing or decreasing the activity of (4), respectively;

(11) reducing the activity of (4) comprising contacting a cell with (I) that binds to (1) or (4);

(12) a pharmaceutical composition comprising (2), or (I);

(13) use of (2) or (I) to produce a medicament for modulating the activity of (4) in a disease;

(14) a cDNA encoding a polypeptide having a sequence of S1 or S3;

(15) a fusion protein comprising (4);

(16) detecting a coding sequence for (4) comprising hybridizing a polynucleotide comprising 11 contiguous nucleotides of S4 to nucleic acid material of a biological sample, forming a hybridization complex and detecting the complex;

(17) a kit for (16), comprising the polynucleotide of 11 nucleotides and instructions;

(18) detecting (4) comprising contacting a biological sample with (I) that specifically binds to (4) to form a complex and detecting the complex;

(19) a kit for (18), comprising an antibody that binds (4) and instructions;

(20) screening for agents which modulate activity of (4), comprises contacting the test compound with a product encoded by (1) and detecting binding;

(21) treating a sphingosine kinase-like protein dysfunction related disease, such as, cancer, asthma, allergy, an autoimmune disease, or a central or peripheral nervous system disorder, comprising administering (I).

ACTIVITY - Cytostatic; antiasthmatic; antiallergic; immunosuppressive; nootropic; neuroprotective; anti-Parkinsonian. Experimental protocols are described but no specific results are given.

MECHANISM OF ACTION - Gene therapy; antisense gene therapy; sphingosine kinase-like protein regulator.

USE - (I) and a nucleic acid expression vector comprising a nucleic acid encoding a sphingosine kinase-like protein polypeptide, are used for producing a medicament for modulating the activity of a sphingosine kinase-like protein in a disease, such as cancer, asthma, allergy, an autoimmune disease, or a central or peripheral nervous system disorder. (I) is used to detect the presence of a sphingosine kinase-like protein polypeptide in a biological sample (all claimed). An example of a nervous system disorder that can be treated is Parkinson's disease.

Dwg.0/6

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B04-B03C; B04-E03E; B04-E05; B04-E06; B04-E07; B04-E08; B04-F0100E; B04-G03; B04-L04; B04-L0400E; B04-N08; B11-C07A; B11-C08E; B11-C08E3; B11-C08E5; B12-K04E; B12-K04F; B14-D06; B14-G02A; B14-G02D; B14-H01; B14-J01; B14-J01A3; B14-J02; B14-K01A; B14-S03; B14-S03B; D05-C03D; D05-H09; D05-H11; D05-H12A; D05-H12D2; D05-H12D4; D05-H12E; D05-H14; D05-H17A3; D05-H17C

TECH UPTX: 20020626

TECHNOLOGY FOCUS - BIOLOGY - Preferred Nucleic Acid: The cDNA of (14), comprises or consists of a sequence of 979 or 4413 base pairs (bp), given

in the specification.
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: In (6) and (16), the nucleic acid material of the biological sample is amplified before hybridization. In screening for agents that modulate (4), the step of contacting is in a cell, which may be in vitro. Alternatively, contacting may be in a cell-free system. The polypeptide or the test compound comprises a detectable label. The test compound displaces a labeled ligand, bound to the polypeptide. The polypeptide or test compound is bound to a solid support. In (20), the product may be RNA. In (11), the cell is in vitro or in vivo. In (21), (I) is identified by (20), Preferred Reagent: In (18), (I) is an antibody. In (11), the reagent may be a polypeptide, antibody, RNA, antisense oligonucleotide, or ribozyme.
ABEX UPTX: 20020626
ADMINISTRATION - Administration is by oral, intravenous, intramuscular, intraarterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, tntraperitoneal, intranasal, parenteral, topical, sublingual, or rectal routes. Dose is 0.1 microgram - 1 g.

EXAMPLE - Purified **sphingosine** kinase-like protein polypeptides having a sequence of 326, 537, or 562 amino acids, given in the specification and comprising a glutathione-S-transferase protein, were absorbed onto glutathione-derivatized wells and contacted with test compounds from a small molecule library at pH 7.0 in physiological buffer solution. The test compounds comprises a fluorescent tag. The samples were incubated for 5 minutes to 1 hour and control samples were incubated in the absence of a test compound. The buffer solution containing the test compounds were washed from the wells. Binding of a test compound to the polypeptides was detected by fluorescence of the contents of the wells. A test compound that increased the fluorescence in a well by 15 % relative to a well in which a test compound was not incubated was identified as a compound which bound to the polypeptide.

L161 ANSWER 31 OF 127 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-130896 [17] WPIX
DOC. NO. CPI: C2002-040274
TITLE: Novel **sphingosine** kinase variants which exhibit **reduced** catalytic activity useful for **modulating** cellular functional activity and treating or preventing inflammatory, degenerative diseases and neoplastic conditions.
DERWENT CLASS: B04 D16
INVENTOR(S): MORETTI, P; PITSON, S; VADAS, M; WATTENBERG, B; XIA, P; D'ANDREA, R; GAMBLE, J; ZEBOL, J; DANDREA, R
PATENT ASSIGNEE(S): (MEDV-N) MEDVET SCI PTY LTD
COUNTRY COUNT: 97
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2002000887	A1	20020103	(200217)*	EN	104	C12N015-54
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW						
AU 2001065699	A	20020108	(200235)			C12N015-54
NO 2002006265	A	20030224	(200321)			C12N000-00
EP 1299548	A1	20030409	(200325)	EN		C12N015-54
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT						

	RO	SE	SI	TR			
CN 1444654		A	20030924	(200382)			C12N015-54
JP 2004500903		W	20040115	(200410)		150	C12N015-09
ZA 2003000214		A	20040630	(200448)		118	C12N000-00
BR 2001012059		A	20040727	(200452)			C12N015-54
NZ 523343		A	20050324	(200523)			C12N015-54
MX 2002012924		A1	20040801	(200548)			A61K038-45

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002000887	A1	WO 2001-AU730	20010620
AU 2001065699	A	AU 2001-65699	20010620
NO 2002006265	A	WO 2001-AU730	20010620
		NO 2002-6265	20021227
EP 1299548	A1	EP 2001-942904	20010620
		WO 2001-AU730	20010620
CN 1444654	A	CN 2001-813405	20010620
JP 2004500903	W	WO 2001-AU730	20010620
		JP 2002-506202	20010620
ZA 2003000214	A	ZA 2003-214	20030108
BR 2001012059	A	BR 2001-12059	20010620
		WO 2001-AU730	20010620
NZ 523343	A	NZ 2001-523343	20010620
		WO 2001-AU730	20010620
MX 2002012924	A1	WO 2001-AU730	20010620
		MX 2002-12924	20021219

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001065699	A	Based on	WO 2002000887
EP 1299548	A1	Based on	WO 2002000887
JP 2004500903	W	Based on	WO 2002000887
BR 2001012059	A	Based on	WO 2002000887
NZ 523343	A	Div in	NZ 535290
		Based on	WO 2002000887
MX 2002012924	A1	Based on	WO 2002000887

PRIORITY APPLN. INFO: AU 2001-2749 20010129;
AU 2000-8408
20000628; AU 2000-8699
20000711; AU 2000-9980
20000908

INT. PATENT CLASSIF.:
MAIN: A61K038-45; C12N000-00; C12N015-09; C12N015-54
SECONDARY: A61K038-43; **A61P001-04; A61P007-00;**
A61P009-10; A61P011-06;
A61P019-02; A61P025-00;
A61P029-00; A61P035-00;
A61P043-00; C12N009-10;
C12N009-12; C12Q001-02; C12Q001-48

BASIC ABSTRACT:
WO 200200887 A UPAB: 20020313
NOVELTY - A **sphingosine** kinase variant (I), comprising a mutation in a **sphingosine** kinase binding region defined by amino acids 16-153 or a ATP binding site region (or their functionally equivalent regions), where the variant exhibits ablated or reduced

catalytic activity relative to wild-type SK, or a derivative, homolog, analog, chemical equivalent or mimetic of the SK variant, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated nucleic acid molecule (II), its derivative or equivalent, comprising a nucleotide sequence encoding or complementary to a sequence encoding (I);

(2) detecting an agent capable of modulating the interaction of FOSK (friends of SK) with SK or its functional equivalent or derivative, by contacting a cell or its extract containing the SK or FOSK or its functional equivalent or derivative with a putative agent and detecting an altered expression phenotype associated with the interaction;

(3) detecting an agent capable of binding or otherwise associating with the SK region defined by amino acid 16-153 (or its functional equivalent or derivative), by contacting a cell containing the amino acid region with a putative agent and detecting an altered expression phenotype associated with modulation of the function of SK;

(4) analyzing, designing and/or modifying an agent capable of interacting with SK region defined by amino acid 16-153 or its derivative and modulating a functional activity associated with SK, by contacting SK or its derivative with a putative agent and assessing the degree of interactive complementarity of the agent with the binding site;

(5) an agent (II) identified by the method of (2), (3) or (4); and

(6) a pharmaceutical composition comprising (I) or (II).

ACTIVITY - Antiinflammatory; Antirheumatic; Antiarthritic; Cytostatic; Antiasthmatic; Antiatherosclerotic; Neuroprotective; Antibacterial; Immunosuppressive; Osteopathic.

No biological data is given.

MECHANISM OF ACTION - Modulator of SK/FOSK interactivity; Inhibitor of wild-type SK activation; Regulator of cellular functional activity including chemokine, cytokine and inflammatory modulator production; gene therapy.

USE - (I) and (II) are useful for modulating cellular functional activity, down-regulating wild-type SK baseline activity and/or preventing wild-type SK activation. (I) and (II) are also useful for treatment and/or prophylaxis of a condition in a mammal, characterized by aberrant, unwanted or inappropriate cellular activity, and in the manufacture of a medicament for modulating cellular functional activity. (All claimed). (I) is useful in therapeutically or prophylactically treating inflammatory diseases (e.g. rheumatoid arthritis, inflammatory bowel disease), neoplastic conditions (e.g. solid cancer), asthma, atherosclerosis, meningitis, multiple sclerosis, septic shock, osteoarthritis, and other degenerative diseases.

Dwg.0/15

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B04-E02E; B04-F01; B04-L04; B11-C08E1; B11-C08E3; B12-K04E; B14-C06; B14-C09A; B14-C09B; B14-E10C; **B14-F07**; B14-H01; B14-H01B; B14-K01A; B14-N01; B14-N16; B14-S01; B14-S03A; B14-S05; D05-A02B; D05-H08; D05-H09; D05-H12B1

TECH UPTX: 20020313

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preparation: (I) is derived from natural or recombinant sources.

Preferred Variant: SK is human SK and comprises a single or multiple amino acid substitution, addition and/or deletion. The SK binding region is defined by amino acids 70-90, preferably 79-84. The variant exhibits ablated catalytic activity, particularly a **reduced** capacity to phosphorylate **sphingosine** to **sphingosine** 1-phosphate.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) may also be chemically synthesized.

ABEX UPTX: 20020313

SPECIFIC MUTANTS - (I) comprises one or more of the amino acid substitutions chosen from G82D, G82A, G26D, S79D, G80D, K103A, G111D, G113D, G26A, K27A, K29A, S79A, G80A, K103R and G111A (claimed).

ADMINISTRATION - Administered by oral, intravenous, intranasal, intraperitoneal, intramuscular, subcutaneous, intradermal or suppository route at a dose of 0.1-1 mg/kg/day.

EXAMPLE - The **sphingosine** kinase (SK-1) cDNA Pitson et al., 2000 was cloned into pALTER site directed mutagenesis vector. Single-stranded DNA was prepared and used as template for oligonucleotide directed mutagenesis. The mutagenic oligonucleotide (5'-CTGGAGACGATCTGATGCAC) was designed to generate the G82D mutant, substitution of the glycine at position 82 to aspartic acid. The mutagenic oligonucleotide (5'-GTCTGGAGATGCATTGATGCACG-3') was designed to generate the SK(G82A) mutant, substitution of the glycine at position 82 to alanine. The mutants were sequenced to verify incorporation of the desired modification and sub-cloned into pcDNA3. The expression construct was transfected by calcium phosphate precipitation into HEK293T cells. The G82DSK by itself had no SK activity and did not suppress endogenous baseline SK activity, however it totally suppressed the increases in SK activity seen after treatment of cells with activating agents such as tumor necrosis factor (TNF), interleukin-1 (IL-1) and PMA (phorbol-12-myristate-13-acetate). G82DSK inhibited SK stimulated by the oncogene Ras and suppressed in vitro and in vivo markers of oncogenesis. The inhibitor was specific as it didn't **depress** the activation of another enzyme protein kinase C or **sphingomyelinase.** Human SK(G82A) had catalytic activity much lower than the wild-type hSK. Analysis of the substrate kinetics of hSK(G82A) showed that this mutant had considerably lower affinity for ATP than the wild-type hSK, while the affinity for **sphingosine** remained unaffected. The kinetic data indicated that Gly82 was involved in ATP binding and this residue was a part of the ATP-binding site of HSK.

L161 ANSWER 32 OF 127 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-478846 [51] WPIX
DOC. NO. CPI: C2002-136189
TITLE: New isolated **sphingosine** kinase, useful in identifying **modulators** for treating e.g. cancer, also related nucleic acid, vectors and transformed cells.
DERWENT CLASS: B04 D16
INVENTOR(S): SPIEGEL, S
PATENT ASSIGNEE(S): (SPIE-I) SPIEGEL S
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 2002042358	A1	20020411	(200251)*		24	A61K031-00
US 6830916	B2	20041214	(200501)			C12N009-48<--

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE	
US 2002042358	A1 Provisional	US 2000-186352P	20000302	<--
		US 2001-796487	20010302	
US 6830916	B2 Provisional	US 2000-186352P	20000302	<--

CIP of US 2000-530868 20000505 <--
US 2001-796487 20010302

PRIORITY APPLN. INFO: **US 2000-186352P 20000302**; US 2001-796487 20010302; **US 2000-530868 20000505**
INT. PATENT CLASSIF.:
MAIN: A61K031-00; **C12N009-48**
SECONDARY: C07H021-04; C12N001-20; C12N005-06; **C12N009-12**; C12N015-00; C12Q001-00

BASIC ABSTRACT:

US2002042358 A UPAB: 20020812

NOVELTY - Isolated **sphingosine** kinase (SPHK) DNA (I) and parts of it.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) cells transfected with (I);
(2) testing compounds (M1) for their effect on SPHK activity;
(3) recombinant DNA comprising (I) and a vector;
(4) preparation (M2) of SPHK peptides (II) by culturing cells of (1);
(5) isolated (II) produced by M2;
(6) screening (M3) for compounds that reduce, eliminate or promote SPHK activity;
(7) detecting (M4) SPHK by reaction with antibodies (Ab);
(8) agents (A) that inhibit or promote SPHK activity;
(9) detecting (M5) SPHK by polymerase chain reaction;
(10) diagnostic kit for detecting SPHK RNA/cDNA comprising primers or oligonucleotides;
(11) measuring (M6) **sphingosine**-1-phosphate (SPP);
(12) decreasing (M7) cell proliferation by reducing SPHK activity or expression; and
(13) reducing (M8) cell death by increasing SPHK activity or expression.

ACTIVITY - Cytostatic; vasotropic; antidiabetic; neuroprotective. No supporting data is given.

MECHANISM OF ACTION - **Modulating** production of **sphingosine**-1-phosphate, a **regulator** of mitogenesis, apoptosis, atherosclerosis and inflammatory reactions. No supporting data is given.

USE - Cells transformed with (I) are used to screen for agents that reduce, eliminate or promote SPHK activity. Agents that inhibit activity are useful for decreasing cell proliferation, e.g. for treating cancer, and for treating diseases associated with abnormal migration and motility of cells, e.g. **restenosis** or diabetic neuropathy. Agents that increase activity are used to reduce cell death (claimed). Antibodies (Ab) raised against SPHK, and primers or oligonucleotides derived from (I) are useful for diagnosis; Ab are also useful as therapeutic inhibitors.

Dwg.0/3

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B04-B03C; B04-C01G; B04-E03E; B04-E05; B04-E08; B04-F0100E; B04-G01; B04-L0400E; B04-M01; B11-C08E; B12-K04E; B12-K04F; **B14-F02**; B14-H01; B14-N16; D05-H09; D05-H11; D05-H12A; D05-H12D1; D05-H12E; D05-H14; D05-H17A3

TECH UPTX: 20020812

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Nucleic Acid: (I) is (i) human or (ii) murine, and then comprises the sequences of genbank AF068748

or 068749, or their fragments of at least 30 nucleotides. Particularly (I) encodes a 381 amino acid SPHK, or its natural or synthetic variants, or fragment of at least 10 amino acids. (I) may be incorporated into prokaryotic or eukaryotic vectors.
Preparation: A 49 kD SPHK was isolated from rat kidney and the sequences of several tryptic peptides determined. These were used in homology searching to identify two murine sequences of 388 and 381 amino acids (mSPHK1a and 1b). The sequence for humanSPHK1 was obtained by reverse transcription polymerase chain reaction on RNA from HEK293 cells and a gene-specific antisense primer. The cDNA formed was extended by the rapid amplification of cDNA ends process and the complete sequence has been deposited as AF238083. Once isolated, the human cDNA can be cloned into e.g. pcDNA3.1 or pCR3.1 for expression in HEK293 cells.
Preferred Method: In M1, a test compound is incubated with (i) **control** cells and (ii) cells transformed to express (I) so that **sphingosine** metabolites (SM) are formed, and the levels of SM and SPHK are measured and compared. In M3, cells transfected with the vector of (3) are incubated with test compound and any change in SPHK-dependent phosphorylation of lipids, relative to **controls**, is measured. In M1, SPP is isolated from other phospholipids in a sample, converted to **sphingosine**, and this phosphorylated using a detectably labeled phosphate. The amount of label that becomes incorporated is then measured.
ABEX UPTX: 20020812
WIDER DISCLOSURE - Also disclosed are antibodies (Ab) specific for SPHK.

ADMINISTRATION - No administration or dosage details are given.

EXAMPLE - No suitable example is given.

L161 ANSWER 33 OF 127 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-626376 [72] WPIX
DOC. NO. NON-CPI: N2001-466934
DOC. NO. CPI: C2001-186633
TITLE: Novel human or murine **sphingosine** kinase type 2 isoform polypeptide useful for treatment or amelioration of disease resulting from increased cell death or decreased cell proliferation.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): KOHAMA, T; SPIEGEL, S; SARAH, S; TAKAFUMI, K
PATENT ASSIGNEE(S): (KOHA-I) KOHAMA T; (SANY) SANKYO CO LTD; (SPIE-I) SPIEGEL S; (GEOU) UNIV GEORGETOWN
COUNTRY COUNT: 96
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2001074837	A1	20011011	(200172)*	EN	117	C07H021-04
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW						
AU 2001051002	A	20011015	(200209)			C07H021-04
US 2002042101	A1	20020411	(200227)			C12P021-02
NO 2002004727	A	20021203	(200305)			C07H000-00
EP 1268509	A1	20030102	(200310)	EN		C07H021-04
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR						
KR 2002093017	A	20021212	(200328)			C12N015-54

CZ 2002003282	A3	20030514	(200337)			C07H021-04
HU 2003001691	A2	20030828	(200363)			C07H021-04
CN 1443192	A	20030917	(200382)			C07H021-04
JP 2004500117	W	20040108	(200410)		205	C12N015-09
ZA 2002007930	A	20040331	(200426)		135	C07H000-00
BR 2001009827	A	20040706	(200445)			C07H021-04
US 6800470	B2	20041005	(200465)			C12N009-12<--
US 2004203104	A1	20041014	(200468)			C12N009-12<--
IN 2002001231	P2	20050311	(200555)	EN		C07H021-04
MX 2002009781	A1	20041001	(200557)			A61K031-70
AU 2001251002	B2	20051020	(200615)			C07H021-04

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE	
WO 2001074837	A1		WO 2001-US9664	20010326	
AU 2001051002	A		AU 2001-51002	20010326	
US 2002042101	A1	Provisional	US 2000-194318P	20000403	<--
			US 2001-817676	20010326	
NO 2002004727	A		WO 2001-US9664	20010326	
			NO 2002-4727	20021002	
EP 1268509	A1		EP 2001-924340	20010326	
			WO 2001-US9664	20010326	
KR 2002093017	A		KR 2002-713149	20021001	
CZ 2002003282	A3		WO 2001-US9664	20010326	
			CZ 2002-3282	20010326	
HU 2003001691	A2		WO 2001-US9664	20010326	
			HU 2003-1691	20010326	
CN 1443192	A		CN 2001-810585	20010326	
JP 2004500117	W		JP 2001-572526	20010326	
			WO 2001-US9664	20010326	
ZA 2002007930	A		ZA 2002-7930	20021002	
BR 2001009827	A		BR 2001-9827	20010326	
			WO 2001-US9664	20010326	
US 6800470	B2	Provisional	US 2000-194318P	20000403	<--
			US 2001-817676	20010326	
US 2004203104	A1	Provisional	US 2000-194318P	20000403	<--
		Div ex	US 2001-817676	20010326	
			US 2004-830677	20040422	
IN 2002001231	P2		WO 2001-US9664	20010326	
			IN 2002-KN1231	20020927	
MX 2002009781	A1		WO 2001-US9664	20010326	
			MX 2002-9781	20021003	
AU 2001251002	B2		AU 2001-251002	20010326	

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001051002	A	Based on	WO 2001074837
EP 1268509	A1	Based on	WO 2001074837
CZ 2002003282	A3	Based on	WO 2001074837
HU 2003001691	A2	Based on	WO 2001074837
JP 2004500117	W	Based on	WO 2001074837
BR 2001009827	A	Based on	WO 2001074837
MX 2002009781	A1	Based on	WO 2001074837
AU 2001251002	B2	Based on	WO 2001074837

PRIORITY APPLN. INFO: US 2001-817676 20010326;

US 2000-194318P
20000403; US 2004-830677
20040422

INT. PATENT CLASSIF.:
MAIN: A61K031-70; C07H000-00; C07H021-04; **C12N009-12**; C12N015-09; C12N015-54; C12P021-02
SECONDARY: A61K038-45; A61K038-48; A61K038-51; A61K039-395; A61K045-00; **A61P009-00**; **A61P009-14**; **A61P025-28**; **A61P029-00**; **A61P035-00**; **A61P043-00**; C07H004-04; C12N001-15; C12N001-16; C12N001-19; C12N001-20; C12N001-21; C12N005-00; C12N005-04; C12N005-06; C12N005-10; C12N015-63; C12P021-06; C12Q001-48; C12Q001-68; G01N033-15; G01N033-50; G01N033-53; G01N033-573

BASIC ABSTRACT:

WO 200174837 A UPAB: 20011206

NOVELTY - A human or murine **sphingosine** kinase type 2 isoform (SPHK2) polypeptide (I) comprising a sequence of 618 or 617 amino acids fully defined in the specification, respectively, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated and purified DNA (II) which encodes a mammalian **sphingosine** kinase type 2 isoform, where (II) comprises a sequence selected from the sequence of Genbank Accession Number bankit325787 and the sequence of Genbank Accession Number bankit325752;

(2) a peptide (III) encoded by (II);

(3) a recombinant DNA construct (IV) comprising a vector and (II);

(4) a host cell (V) transformed with (IV);

(5) production of (I);

(6) detecting (M1) an agent or a drug which **inhibits** or promotes **sphingosine** kinase type 2 activity involves providing (IV) into a cell such that **sphingosine** kinase type 2 isoform is produced in the cell, adding at least one drug or agent to the cell, and detecting whether or not the drug or agent **inhibits** or promotes **sphingosine** kinase type 2 activity by measuring **sphingosine** kinase-dependent phosphorylation of lipids in the cells and comparing the resultant measurement to a **control** which did not receive the drug or agent, where a decrease in the amount of **sphingosine** kinase-dependent phosphorylation of lipids as compared to the **control** indicates an **inhibitory** drug or agent, or an increase in the amount of **sphingosine** kinase-dependent phosphorylation of lipids in the cell as compared to the **control** indicates a stimulatory drug or agent;

(7) an agent or drug (VI) detected by M1

(8) a composition (VII) for treating or ameliorating a disease resulting from increased cell death or decreased cell proliferation comprises a pharmaceutically effective amount of (III);

(9) screening (M2) agents or drugs which **reduce** or eliminate **sphingosine** kinase type 2 activity, involves detecting a decrease in **sphingosine** kinase type 2 enzyme activity in the presence of the agent or drug;

(10) detecting (M3) the presence of a **sphingosine** kinase type 2 isoform in a sample involves contacting a sample with antibodies which recognize **sphingosine** kinase type 2 and detecting the presence or absence of a complex formed between **sphingosine** kinase type 2 and antibodies specific for it, or by subjecting the sample to a polymerase chain reaction and detecting for the presence of **sphingosine** kinase type 2;

(11) a diagnostic kit (VIII) for detecting **sphingosine**

kinase type 2 RNA/cDNA in a sample comprises primers or oligonucleotides specific for **sphingosine** kinase type 2 RNA or cDNA suitable for hybridization to **sphingosine** kinase type 2 RNA or cDNA and/or amplification of **sphingosine** kinase type 2 sequences and suitable ancillary reagents; and

(12) treating or ameliorating (M4) a disease resulting from decreased cell death or increased proliferation, or a disease resulting from abnormal migration or motility of cells, where the disease resulting from abnormal migration or motility of cells is selected from cancer, **restenosis**, and diabetic neuropathy, involves administering to the mammal a pharmaceutically effective amount of an antibody to (III).

ACTIVITY - Cytostatic; antiarteriosclerotic; **cerebroprotective**; nootropic; neuroprotective; **cardiant**; antidiabetic; antiinflammatory; antiangiogenesis.

MECHANISM OF ACTION - **Sphingosine** kinase type 2 activity **modulator** (claimed). No supporting data is given.

USE - (III) is useful for regulating a biological process in a mammal, where the biological process is selected from mitogenesis, apoptosis, neuronal development, chemotaxis, **angiogenesis** and inflammatory responses, preferably **angiogenesis.** (III) is useful for treatment or amelioration of a disease resulting from increased cell death or decreased cell proliferation (claimed). (I) is useful as a diagnostic tool, for producing **sphingosine**-1-phosphate (SPP), for measuring levels of SPP in a sample, as a therapeutic agent to **reduce** cell death and/or increase cell proliferation, and to identify **inhibitors** of **sphingosine** kinase type 2 activity. (II) is useful to design primers for detecting **sphingosine** kinase type 2. (VII) is useful in the treatment or amelioration of diseases such as cancer, atherosclerosis, and neurodegenerative disorders such as **stroke** and Alzheimer's disease.

Dwg.0/6

FILE SEGMENT: CPI EPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B04-B03C; B04-E02E; B04-E03E; B04-E05; B04-E08; B04-F0100E; B04-G03; B04-L04; B11-C07A; B11-C08; B12-K04; B14-C03; **B14-F02**; **B14-F07** ; B14-H01; B14-J01; B14-J01A4; B14-L06; B14-N16; D05-H09; D05-H11; D05-H12A; D05-H12E; D05-H14; D05-H17A3
EPI: S03-E14H4

TECH UPTX: 20011206

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preparation: (I) is prepared by culturing (V) under conditions such that (II) is expressed (claimed).
Preferred Polynucleotide: (II) encodes a mouse or human **sphingosine** kinase type 2 isoform comprising a sequence of 617 or 618 amino acids fully defined in the specification.
Preferred Construct: In (IV), the vector is an expression vector, preferably a prokaryotic or eukaryotic vector.
Preferred Cell: (V) is a prokaryotic or eukaryotic cell.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) may also be prepared by standard chemical synthesis.

ABEX UPTX: 20011206

WIDER DISCLOSURE - Also disclosed as new are:
(1) an isolated nucleic acid molecule comprising polynucleotides which hybridize under stringent conditions to (II);
(2) a variant of (II), which encodes portions, analogs or derivatives of (I); and
(3) a monoclonal or polyclonal antibody specific for (I).

ADMINISTRATION - A pharmaceutical composition comprising (VI) is administered by topical, transdermal, intraperitoneal, oral, rectal or parenteral route at a dose of 1 pg/kg-10 mg/kg.

EXAMPLE - cDNA cloning of human **sphingosine** kinase-2 (hSPHK2) was as follows. Poly (A)+ RNA from HEK293 cells was used for a 5' rapid amplification of cDNA ends (RACE) reaction. Target specific antisense primers (h-GSP1: 5'-CCCACTCACTCAGGCT), h-GSP2: 5'GAAGGACAGCCCAGCTTCAGAG, and h-GSP3, 5'-ATTGACCAATAGAAGCAACC) were designed according to the sequence of a human EST (expressed sequence tag) clone (accession number AA295570). A first strand cDNA was synthesized with 5 microg or HEK293 mRNA and h-GSP1. This cDNA was used as a template in an initial PCR (polymerase chain reaction) using 5'RACE Abridged Anchor Primer and h-GSP2. Then, a nested PCR was carried out using the AUAP primer and h-GSP3. The resulting PCR products were cloned into pCR2.1 and sequenced. The PCR products were subcloned into pCR3.1 and pcDNA 3 expression vectors.

L161 ANSWER 34 OF 127 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-300510 [31] WPIX
DOC. NO. NON-CPI: N2001-215617
DOC. NO. CPI: C2001-092366
TITLE: New human **sphingosine** kinase type I gene for screening drug candidates particularly **inhibitors** used for **preventing** or treating e.g. atherosclerosis, thrombosis, asthma and diabetes.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): ALLEN, J; GOSINK, M; MELENDEZ, A J; TAKACS, L
PATENT ASSIGNEE(S): (WARN) WARNER LAMBERT CO
COUNTRY COUNT: 95
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2001031029	A2	20010503	(200131)*	EN	90	C12N015-54
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW						
AU 2001010202	A	20010508	(200149)			C12N015-54
BR 2000015138	A	20020716	(200255)			C12N015-54
EP 1228221	A2	20020807	(200259)	EN		C12N015-54
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI						
JP 2003512072	W	20030402	(200325)		94	C12N015-09
MX 2002004294	A1	20021101	(200376)			A01K067-027

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE	
WO 2001031029	A2	WO 2000-EP9498	20001027	<--
AU 2001010202	A	AU 2001-10202	20001027	<--
BR 2000015138	A	BR 2000-15138	20001027	<--
		WO 2000-EP9498	20001027	<--
EP 1228221	A2	EP 2000-971299	20001027	<--
		WO 2000-EP9498	20001027	<--

JP 2003512072	W	WO 2000-EP9498	20001027	<--
		JP 2001-533164	20001027	<--
MX 2002004294	A1	WO 2000-EP9498	20001027	<--
		MX 2002-4294	20020429	

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001010202	A Based on	WO 2001031029
BR 2000015138	A Based on	WO 2001031029
EP 1228221	A2 Based on	WO 2001031029
JP 2003512072	W Based on	WO 2001031029
MX 2002004294	A1 Based on	WO 2001031029

PRIORITY APPLN. INFO: **US 2000-180525P 20000207; US 1999-162307P 19991028**

INT. PATENT CLASSIF.:

MAIN: A01K067-027; C12N015-09; C12N015-54

SECONDARY: C07K016-40; C12N001-15; C12N001-19; C12N001-21; C12N005-10; **C12N009-12**; C12N015-11; C12P021-02; C12Q001-48; C12Q001-68; G01N033-15; G01N033-50; G01N033-53; G01N033-566; G01N033-68

ADDITIONAL: A61K045-00; **A61P003-06**; **A61P003-10**; **A61P007-02**; **A61P009-02**; **A61P009-10**; **A61P011-00**; **A61P011-06**; **A61P017-00**; **A61P017-02**; **A61P017-06**; **A61P019-02**; **A61P025-00**; **A61P025-28**; **A61P029-00**; **A61P035-00**; **A61P037-02**; **A61P043-00**

BASIC ABSTRACT:

WO 200131029 A UPAB: 20010607

NOVELTY - A purified or isolated nucleic acid encoding a human **sphingosine** kinase (hSK), which together with its encoded protein are applicable in screening drug candidates particularly **inhibitors** for preventing or treating e.g. atherosclerosis, thrombosis, asthma and diabetes, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a purified or isolated polynucleotide encoding a hSK having not less than 90 % amino-acid identity with a sequence of 384 amino acids, given in the specification;

(2) a polynucleotide having a sequence of 240 base pairs (bp), given in the specification, or a polynucleotide hybridizable with it;

(3) a polynucleotide with not less than 10 consecutive nucleotides in a sequence of 1719, 1155 or 240 bp, given in the specification;

(4) a recombinant vector containing the nucleic acid;

(5) a recombinant host cell comprising the nucleic acid or recombinant vector;

(6) an oligonucleotide comprising the antisense strand of any of the above nucleic acids;

(7) a transgenic animal containing the nucleic acid;

(8) a transgenic mouse containing the nucleic acid;

(9) a purified or isolated recombinant polypeptide with the amino-acid sequence of hSK;

(10) a purified or isolated recombinant polypeptide with a sequence of 80 amino acids, given in the specification;

(11) amplifying a nucleic acid encoding a hSK comprising:
(a) contacting a test sample suspected of containing hSK nucleic acid, its fragment or variant or a sequence complementary to it, with an amplification reaction reagent containing the above polynucleotides as primers for hybridization of the hSK nucleic acid region to be amplified under stringent conditions; and
(b) optionally detecting the amplification products;
(12) a kit for amplification containing the oligonucleotide primers and reagents for performing the amplification;
(13) producing an amino-acid sequence of 384 amino acids, given in the specification, comprising:
(a) producing a recombinant vector or transformant host cell;
(b) culturing the transformant;
(c) harvesting the culture medium obtained or lyzing the host cell, for example by sonication or osmotic shock; and
(d) separating or purifying from the medium, or from the pellet of the resultant host cell lysate to produce the polypeptide, eventually tagged;
(14) an antibody directed against the polypeptide;
(15) screening candidate molecules particularly as inhibitors of hSK comprising:
(a) mixing a recombinant polypeptide with **sphingosine**, labeled ATP and a sample; and
(b) measuring the level of conversion of **sphingosine** into labeled **sphingosine**-1-phosphate; and
(16) a kit for screening the candidate molecules comprising the recombinant polypeptide and optionally labeled ATP and **sphingosine**
.

ACTIVITY - Antiarteriosclerotic; thrombolytic; anticoagulant; antilipemic; antidiabetic; **cerebroprotective**; neuroprotective; antipsoriatic; antiinflammatory; antiarthritic; antiasthmatic; cytostatic; **cardiant**; vulnerary. No biological data is given.

MECHANISM OF ACTION - Human **sphingosine** kinase.

USE - The gene and encoded polypeptide are applicable in screening drug candidates particularly inhibitors for preventing or treating e.g. atherosclerosis, fibrosis, thrombosis, dyslipidemia, diabetes especially type I diabetes, **stroke**, multiple sclerosis, psoriasis, epidermodysplasia verruiformis, inflammatory arthritis, T helper-1 related diseases, chronic obstructive disease, asthma, cancer, hemostatis, **coronary artery** disease, hematopoietic disorders like leukemia, **myocardial** infarction, natural wound healing processes and embryogenesis.

Dwg.0/18

FILE SEGMENT: CPI EPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B04-B03C; B04-C01G; B04-E03E; B04-E05; B04-E08; B04-F0100E; B04-G03; B04-L04; B04-L0400E; B04-P0100E; B04-P01A0E; B11-B; B11-C08; B11-C08E3; B11-C08E5; B12-K04E; B12-K04F; B14-C03; B14-C09; **B14-F01**; **B14-F02**; **B14-F04** ; **B14-F06**; **B14-F07**; B14-H01; B14-H01A; B14-K01A; B14-N16; B14-N17B; B14-N17C; B14-S01; B14-S04; D05-C03D; D05-H09; D05-H11; D05-H12A; D05-H12D1; D05-H12E; D05-H14; D05-H16A; D05-H17A3; D05-H18B
EPI: S03-E14H

TECH UPTX: 20010607
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Nucleic Acid: The nucleic acid comprises a polynucleotide having not less than 90% identity with the sequence of 1719 or 1155 bp or a sequence complementary to it. The

polynucleotide of (3), comprises one of 10 sequences of 27, 31, 30, 20, 29, 32, or 28 bp, given in the specification. The oligonucleotide has a sequence of 21 bp, given in the specification.
Preferred Vector: The recombinant vector is particularly a bacterial vector, or aPGEX vector, or a baculovirus vector, preferably pFastBacHTa, or an eukaryotic vector chosen from pcDNA3, pFLAG and pCMV.
Preferred Polypeptide: The polypeptide has not less than 80 % amino-acid identify with a polypeptide of 384 amino acids, given in the specification, or a sequence complementary to it.
Preparation: The nucleic acid was prepared using standard biochemical techniques.

ABEX UPTX: 20010607
EXAMPLE - No suitable example is given.

L161 ANSWER 35 OF 127 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-281835 [29] WPIX
DOC. NO. CPI: C2001-085768
TITLE: Isolated peptide, capable of protecting cells from apoptosis by inhibiting DAP-kinase, comprises fragments of DAP-kinase.
DERWENT CLASS: B04 D16
INVENTOR(S): BERISSI, H; FRIDKIN, M; KIMCHI, A; RAVEH, T
PATENT ASSIGNEE(S): (MCIN-I) MCINNIS P; (YEDA) YEDA RES & DEV CO LTD
COUNTRY COUNT: 95
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2001026678	A1	20010419	(200129)*	EN	63	A61K038-51
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW						
AU 2001010827	A	20010423	(200147)			A61K038-51
EP 1223970	A1	20020724	(200256)	EN		A61K038-51
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI						
JP 2003516122	W	20030513	(200334)		62	C12N015-09

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE	
WO 2001026678	A1	WO 2000-US28312	20001013	<--
AU 2001010827	A	AU 2001-10827	20001013	<--
EP 1223970	A1	EP 2000-972123	20001013	<--
		WO 2000-US28312	20001013	<--
JP 2003516122	W	WO 2000-US28312	20001013	<--
		JP 2001-529739	20001013	<--

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001010827	A	Based on	WO 2001026678
EP 1223970	A1	Based on	WO 2001026678
JP 2003516122	W	Based on	WO 2001026678

PRIORITY APPLN. INFO: **US 1999-159107P**
19991013
INT. PATENT CLASSIF.:
MAIN: A61K038-51; C12N015-09
SECONDARY: A61K038-00; A61K045-00; **A61P027-02**; **A61P027-06**; **A61P043-00**; C07H021-04; C12N001-20; C12N005-00; C12N005-10; **C12N009-12**; **C12N009-99**; C12N015-00; C12Q001-68; G01N033-15; G01N033-50; G01N033-566
INDEX: C12N005-10; C12Q001-68; C12R001:91; C12R001:91

BASIC ABSTRACT:

WO 200126678 A UPAB: 20010528

NOVELTY - An isolated peptide (P1) capable of protecting cells from apoptosis by inhibiting DAP-kinase, is new.

DETAILED DESCRIPTION - An isolated peptide (P1) capable of protecting cells from apoptosis by inhibiting DAP-kinase, is new.

P1 is selected from:

(a) a peptide consisting of the sequence of (I) from the C-terminal tail of DAP-kinase;

(b) a DAP-kinase peptide fragment of 48 amino acid residues in length which comprises the ankyrin repeats in DAP-kinase;

(c) a DAP-kinase peptide fragment of 55 amino acid residues in length which comprises the linker region of DAP-kinase;

(d) a DAP-kinase peptide fragment of 52 amino acid residues in length which comprises the death domain of DAP-kinase;

(e) a fragment of (a), (b), (c) or (d) which is capable of protecting cells from apoptosis by inhibiting DAP-kinase;

(f) an analog of (a)-(e) which is capable of protecting cells from apoptosis by inhibiting DAP-kinase;

(g) a peptide of (a)-(f) which is extended at one or both of its termini by one to four amino acid residues;

(h) a peptide of (a)-(f) which is extended at one or both of its termini with Asp or Glu residues; or

(i) a derivative of (a)-(h) which is capable of protecting cells from apoptosis.

(I) has the following sequence: Ser-Cys-Asn-Ser-Gly-Thr-Ser-Tyr-Asn-Ser-ILe-Ser-Ser-Val-Val-Ser-Arg.

INDEPENDENT CLAIMS are also included for the following:

(1) a method for inhibiting apoptosis associated with the activity of DAP-kinase, comprising administering an effective amount of P1 to neutralize the effect of DAP-kinase and to inhibit apoptosis associated with DAP-kinase;

(2) a polynucleotide encoding P1;

(3) a vector comprising the polynucleotide of (2);

(4) a host cell transformed with the vector of (3);

(5) a method (M1) for screening fragments of a gene product, mediating a selectable phenotype, for capability of acting in a dominant negative manner when expressed ectopically, comprising:

(a) fragmenting a cDNA encoding a gene product, which mediates a selectable phenotype, to obtain random cDNA fragments;

(b) inserting the random cDNA fragments into an Epstein-Barr virus (EBV)-based episomal shuttle vector capable of propagation in bacterial and mammalian cells to generate a library of random cDNA fragments, where the random cDNA fragments are operably linked to a promoter for expressing the random cDNA fragments and the EBV-based episomal shuttle vector has a selectable marker and an interferon responsive enhancer element which stimulates the expression of the random cDNA fragment from the operably-linked promoter;

(c) transforming mammalian host cells with the library of random cDNA fragments in the EBV-based episomal shuttle vector to obtain transformed

host cells;

(d) selecting for transformed host cells that act in a dominant negative manner to the selectable phenotype of the gene product; and

(e) isolating a cDNA fragment which encodes a peptide fragment of the gene product which acts in a dominant negative manner to the gene product; and

(6) a peptide fragment encoded by the cDNA fragment isolated by M1.

ACTIVITY - Antiapoptotic.

The DAP-kinase 'death domain' and the C-terminal peptide were used in order to assess the participation of DAP-kinase in neuronal cell death. These specific inhibitory protein domains were first tested in neuronal cell lines subjected to undergo apoptosis by **ceramides** and then in primary

neurons aiming at elaborating conditions in which the delivery into primary hippocampal neurons will be as simple as possible. In the first preliminary step, an immortalized human neuroblastoma cell line (BE6C) was transfected with pcDNA3 expression vector carrying either the death domain (CAPk-DD), a non-functional mutated form of the death domain (CAPk-mDD--, see Cohen et al., J. Biol. Chemical 146 (1):141-148, (1999)), for details on the mutation), or with an empty vector. The vectors were co-transfected together with green fluorescent protein (GFP) to visualize the transfectants. FuGENE was used, which yields high transfection efficiencies and low cell toxicity. The chosen apoptotic trigger was **ceramide**, a second messenger produced by **sphingomyelin** hydrolysis **mediating** a large spectrum of apoptotic signals. The C6-**ceramide** derivative was used. This derivative penetrates into cultured cells and turns on apoptotic

pathways. A non-functional analog, dihydro-**ceramide**, was used as a negative control. The titration curves indicated that in neuroblastoma cells, 30 mM of C6-**ceramide** initiated a synchronous type of apoptotic cell death, reaching about 60% cell death in 7-10 hours. The effect was cell density-

dependent. It displayed the classical hallmarks of apoptosis such as PARP cleavage. The cells were exposed to C6-ceramide at 48 hours post transfection. The percent of apoptotic cells among the green cells was assessed under the fluorescence microscope. It was found that expression of the death domain protected the cells by about 45-65% from ceramide-induced cell death. The mutant death domain of DAP-kinase had no death-protective effects and was indistinguishable

from the empty vector.

MECHANISM OF ACTION - DAP-kinase inhibitor.

USE - P1 is useful in the manufacture of a medicament for inhibiting the apoptotic activity of DAP-kinase (claimed).

Dwg.0/9

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B04-C01; B04-E02F; B04-E08; B04-F0100E; B04-F1100E; B11-C08; B12-K04F; B14-L06; D05-H09; D05-H12B2; D05-H12E; D05-H14

TECH UPTX: 20010528

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: In M1, the mammalian host cells are human cells.

Preparation: The peptides were produced using standard genetic engineering techniques.

ABEX UPTX: 20010528

ADMINISTRATION - The peptide can be administered orally or parenterally (e.g. intramuscularly and intravenously). No specified dosage data is given.

EXAMPLE - To isolate biologically active peptides of DAP-kinase, an expression library of its randomly fragmented cDNA was generated and a

positive functional selection in HeLa cells treated with interferon-gamma (IFN-gamma) was carried out. This is the system from which DAP-kinase was originally isolated (Deiss et al., (1991), Genes Dev. 9(1):15-30, 1995). The library was constructed in pTKO1 (Deiss et al., Science 252 (5002):117-120 (1991)), an Epstein-Barr virus (EBV)-based episomal vector, that carries an IFN-responsive enhancer element (ISRE), which stimulates the expression of the library inserts during selection. Into this vector a suitable expression cassette was first introduced, which provided an initiator methionine in a favorable translation initiation context within a Flag epitope, followed by a cloning site and stop codons in all three reading frames. DAP-kinase cDNA fragments generated by incomplete DNase I digestion, and ligated were into the vector. Since the fragmentation and subcloning direction were
both random, it was assumed that half of the fragments were inserted in a sense orientation, and that one-third of these (i.e., about 16% of the total inserts) would be expressed in the correct reading frame.
The DAP-kinase cDNA library was introduced into HeLa cells by transfection, and the cells were then subjected to double selection with hygromycin B and IFN-gamma for three weeks. Cell colonies that survived this prolonged selection were pooled, and episomes were isolated by Hirt's extraction and used to transform bacteria. The cDNA inserts of plasmids from 70 randomly chosen bacterial colonies were amplified by polymerase chain reaction (PCR) and sequenced. Thirteen fragments turned out to be inserted in a sense orientation, and out of the sense fragments, 18 clones encoded peptides in the authentic reading frame of DAP-kinase. Of the 18 clones, four fragments appeared only once, and the rest appeared multiple times corresponding altogether to nine
different fragments. Since the aim was to study the function of different structural motifs of the protein, attention was particularly concentrated on those sense fragments in the correct frame.

L161 ANSWER 36 OF 127 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-468039 [51] WPIX
DOC. NO. CPI: C2001-141459
TITLE: Fermentative isolation of a **sphingosine** kinase **inhibitor** from microorganisms of the Cylindrocarpon genus, for the treatment of **arteriosclerosis**, diabetes mellitus, thrombosis, inflammation, immune disease, cancer, allergy, or **restenosis.**
DERWENT CLASS: B05 D16
PATENT ASSIGNEE(S): (SANY) SANKYO CO LTD
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
JP 2001122846	A	20010508	(200151)*		10	C07C305-24

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE	
JP 2001122846	A	JP 1999-307191	19991028	<--

PRIORITY APPLN. INFO: **JP 1999-307191**
19991028
INT. PATENT CLASSIF.:
MAIN: C07C305-24

SECONDARY: A61K031-603; **A61P003-10**; **A61P007-02**; **A61P009-10**; **A61P029-00**; **A61P035-00**; **A61P035-04**; **A61P037-06**; **A61P037-08**; **A61P043-00**; C12N001-14; **C12N009-99**; C12P011-00
INDEX: C12R001:645; C12P011-00

BASIC ABSTRACT:

JP2001122846 A UPAB: 20010910

NOVELTY - **Sphingosine** kinase **inhibitor** fermentively prepared by cultivation of microorganisms of the Cylindrocarpon genus is new.

DETAILED DESCRIPTION - **Sphingosine** kinase **inhibitor** of formula (1) (F-10163A), its salts, or pharmaceuticals (e.g., **arterioscleoris**-treating agents), prepared by cultivation of microorganisms of the Cylindrocarpon genus (Cylindrocarpon sp.) followed by collection of compound (1) from the cultured broth, is new.

ACTIVITY - Antiarteriosclerotic; antidiabetic; anticoagulant; thrombolytic; antiinflammatory; cytostatic; antiallergic; vasotropic.

No biological data given.

MECHANISM OF ACTION - None given.

USE - The compound (F-10163A) is useful in the prevention and treatment of **arteriosclerosis**, diabetes mellitus, thrombosis, inflammation, immune disease, cancer, cancer metastasis, allergy, and **restenosis** after percutaneous transluminal **coronary** angioplasty (PTCA).

ADVANTAGE - The agent specifically **inhibits** the activity of **sphingosine** kinases.

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B10-A09A; B14-C03; B14-D03; **B14-F01**; **B14-F04**; **B14-F07**; B14-G01; B14-G02; B14-G02A; B14-H01; B14-H01B; B14-S04; D05-C
ABEX UPTX: 20010910

EXAMPLE - Cylindrocarpon sp. SANK 13799 (FERM BP-6852) was cultured on a medium (1000 ml) of dextrin, glycerol, glucose, malt extract, yeast extract, tripton, ammonium nitrate, Na nitrate, K dihydrogenphosphate, Mg sulfate, antifoaming agent CB-422, and deionized water at 23degreesC and 210 rpm for 7 days. The cultured broth (2 L) was centrifuged to separate the cells (500 g, wet) from a supernatant (1.2 L). The cells were extracted with 50 % methanol (1 L) at room temperature for 3 hours. The concentrated extract and the supernatant were combined and subjected to HP-20 and Sephadex column chromatography in aqueous methanol and HPLC column chromatography in MeCN/(5 mM aqueous NaCl) to give, after lyophilization, 25 mg F-10163A.

L161 ANSWER 37 OF 127 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-016227 [02] WPIX
DOC. NO. CPI: C2001-004532
TITLE: Novel **sphingosine** kinase protein and nucleic acid molecules for diagnosis, prophylaxis and treatment of rheumatoid arthritis, asthma, atherosclerosis, inflammation, meningitis, multiple sclerosis and septic shock.
DERWENT CLASS: B04 D16
INVENTOR(S): D'ANDREA, R J; GAMBLE, J R; PITSON, S M; VADAS, M A; WATTENBERG, B W; XIA, P; DANDREA, J; GAMBLE, R; PITSON, M; VADAS, A; WATTENBERG, W; DANDREA, R; GAMBLE, J; PITSON, S; VADAS, M; WATTENBERG, B; DANDREA, R J

PATENT ASSIGNEE(S): (JOHJ) JOHNSON & JOHNSON RES PTY LTD; (JOHJ) JOHNSON & JOHNSON PHARM RES & DEV LLC; (JOHJ) JOHNSON & JOHNSON PHARM R & D LLC
COUNTRY COUNT: 93
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2000070028	A1	20001123	(200102)*	EN	100	C12N009-12<--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW						
AU 2000045239	A	20001205	(200113)			C12N009-12<--
EP 1192247	A1	20020403	(200230)	EN		C12N009-12<--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI						
KR 2002000805	A	20020105	(200244)			C12N009-12<--
JP 2002543831	W	20021224	(200313)		101	C12N015-09
US 6730480	B1	20040504	(200430)			C12Q001-68
US 2004132053	A1	20040708	(200445)			C12Q001-68
NZ 515132	A	20050128	(200513)			C12N009-12<--
AU 780746	B2	20050414	(200530)			C12N009-12<--
EP 1192247	B1	20060412	(200626)	EN		C12N009-12<--
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE						
DE 60027295	E	20060524	(200635)			C12N009-12<--

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE	
WO 2000070028	A1	WO 2000-AU457	20000512	<--
AU 2000045239	A	AU 2000-45239	20000512	<--
EP 1192247	A1	EP 2000-926537	20000512	<--
		WO 2000-AU457	20000512	<--
KR 2002000805	A	WO 2000-AU457	20000512	<--
		KR 2001-714462	20011113	
JP 2002543831	W	JP 2000-618434	20000512	<--
		WO 2000-AU457	20000512	<--
US 6730480	B1	WO 2000-AU457	20000512	<--
		US 2002-959897	20020124	
US 2004132053	A1 Div ex	WO 2000-AU457	20000512	<--
	Div ex	US 2002-959897	20020124	
		US 2003-642289	20030818	
NZ 515132	A	NZ 2000-515132	20000512	<--
		WO 2000-AU457	20000512	<--
AU 780746	B2	AU 2000-45239	20000512	<--
EP 1192247	B1	EP 2000-926537	20000512	<--
		WO 2000-AU457	20000512	<--
DE 60027295	E	DE 2000-00027295	20000512	<--
		EP 2000-926537	20000512	<--
		WO 2000-AU457	20000512	<--

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000045239	A Based on	WO 2000070028

EP 1192247	A1	Based on	WO 2000070028
KR 2002000805	A	Based on	WO 2000070028
JP 2002543831	W	Based on	WO 2000070028
US 6730480	B1	Based on	WO 2000070028
US 2004132053	A1	Div ex	US 6730480
NZ 515132	A	Based on	WO 2000070028
AU 780746	B2	Previous Publ.	AU 2000045239
		Based on	WO 2000070028
EP 1192247	B1	Based on	WO 2000070028
DE 60027295	E	Based on	EP 1192247
		Based on	WO 2000070028

PRIORITY APPLN. INFO: **AU 1999-1504 19990708; AU 1999-339 19990513**

INT. PATENT CLASSIF.:

MAIN: **C12N009-12**; C12N015-09; C12Q001-68

SECONDARY: A61K031-711; A61K038-43; A61K038-45; A61K038-55; A61K039-395; A61K045-00; A61K048-00; **A61P009-10** ; **A61P011-06**; **A61P025-00**; **A61P025-28**; **A61P029-00**; **A61P031-10**; **A61P043-00**; C07H021-04; C07K016-18; C07K016-40; C12N001-20; C12N005-00; C12N005-10; **C12N009-96**; C12N015-00; C12P021-08; C12Q001-48; G01N033-53; G01N033-577

BASIC ABSTRACT:

WO 200070028 A UPAB: 20040621

NOVELTY - An isolated **sphingosine** kinase (SK) protein (I) or its derivative, analog, chemical equivalent or mimetic, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated nucleic acid molecule (II) or its derivative or analog comprising a nucleotide sequence encoding or complementary to a sequence encoding (I);

(2) an agent (III) for use in modulating SK activity or expression;

(3) a pharmaceutical composition comprising (I) or (III);

(4) an isolated antibody (IV) directed to (I) or (II); and

(5) diagnosing or monitoring a mammalian disease condition by screening for (I) in a biological sample isolated from the mammal.

ACTIVITY - Antiarthritic; Antiasthmatic; Antiarteriosclerotic; Antiinflammatory; Neuroprotective; Antibacterial; Immunosuppressive.

No supporting data is given.

MECHANISM OF ACTION - **Modulator** of **sphingosine** kinase activity or expression.

USE - (I), (II) and (III) are useful for **modulating** expression, functional activity or cellular functional activity of **sphingosine** kinase in a subject and also for treating a mammal by **modulating** the activity of SK (claimed). Diseases treated by regulating SK cellular activity include rheumatoid arthritis, asthma, atherosclerosis, inflammation, meningitis, multiple sclerosis and septic shock.

Dwg.0/14

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; DCN

MANUAL CODES: CPI: B04-E03E; B04-G03; B04-G21; B04-G22; B04-L04; B11-C08E; B12-K04A; B14-A01; B14-C03; B14-C06; B14-C09B; **B14-F07**; B14-G02; B14-K01A; B14-S01; B14-S03; D05-H09; D05-H11A; D05-H11B; D05-H12A

TECH UPTX: 20010110

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Nucleic Acid: A nucleic acid molecule (isolated) hybridizable to (II) under low stringency conditions and encoding an amino acid sequence having at least 45% sequence identity or greater to at least 10 contiguous amino acids of (I) is preferred. Preferred Antibody: (IV) is a monoclonal or polyclonal antibody.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) may be prepared by standard synthetic chemistry using solid phase peptide synthesizer.

ABEX UPTX: 20010110

SPECIFIC SEQUENCES - (I) is especially a human **sphingosine** kinase protein having a sequence of 384 amino acids and encoded by a nucleic acid sequence of 1205 base pair defined in the specification (claimed).

ADMINISTRATION - Administered through oral, intravenous, intranasal, intraperitoneal, intramuscular, subcutaneous, intradermal or suppository route or as an implant. Dosage is 0.1 mg-1 mg/kg.

EXAMPLE - The human **sphingosine** kinase (hSK) was amplified from a human umbilical **vein** endothelial cell (HUVEC) lambdaZap cDNA library using polymerase chain reaction (PCR) primers derived from human expressed sequence tag (EST) sequences aligned to the murine **sphingosine** kinase. Primers: 5'-CGGAATTCCCAGTCGGCCGCGGTA-3'; and 5'-TAGAATTCTACCGCGGCCGACTGGCT-3' were used in combination with T3 and T7 primers to generate two overlapping PCR products of 669 base pairs (bp) and 550 bp that represented the 5' and 3' ends of hSK, respectively. These two PCR products were then separately cloned into pGEM4Z and a 584 bp SacII fragment from the 5' hSK PCR clone was then sub-cloned in the correct orientation into the SacII site of the 3' hSK PCR clone, to generate a 1130 bp partial hSK cDNA clone. A full length clone encoding hSK was then generated by sub-cloning a 120 bp EcoRI/StuI fragment from the 669 bp 5' hSK clone into the pGEM4Z-1130 bp clone digested with EcoRI/StuI. For bacterial expression, the full length hSK cDNA was sub-cloned into pGEX4T2. The pGEM4Z-hSK clone was digested with BamHI and blunted with 3U PFU polymerase, a 1163 hSK cDNA was purified and ligated to pGEX4T2 SmaI/XhoI. Recombinant hSK was expressed by transforming the vector into Escherichia coli BL21.

L161 ANSWER 38 OF 127 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-572085 [53] WPIX
DOC. NO. CPI: C2000-170560
TITLE: Anti-lipemic drug comprising an effector of sterol regulatory element binding protein-1 for treating hyperlipoproteinemia, **stroke**, obesity, atherosclerosis, organ transplantation failure and cirrhosis.
DERWENT CLASS: B04 D16
INVENTOR(S): CHATTERJEE, S
PATENT ASSIGNEE(S): (UYJO) UNIV JOHNS HOPKINS
COUNTRY COUNT: 86
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2000050574	A1	20000831	(200053)*	EN	85	C12N009-00<--

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW

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AU 2000032429   A  20000914 (200063)                    <--
EP 1155121      A1 20011121 (200176)  EN       C12N009-00<--
    R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
       RO SE SI
JP 2002537407   W  20021105 (200304)        85 A61K045-00
US 6713057      B1 20040330 (200423)           A61K038-46
AU 776785       B2 20040923 (200480)           C12N009-00<--
US 2005079998   A1 20050414 (200526)           A61K038-00
EP 1155121      B1 20060426 (200629)  EN       A61K031-164
    R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
DE 60027551     E  20060601 (200638)           A61K031-164
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APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE	
WO 2000050574	A1		WO 2000-US4657	20000223	<--
AU 2000032429	A		AU 2000-32429	20000223	<--
EP 1155121	A1		EP 2000-910316	20000223	<--
			WO 2000-US4657	20000223	<--
JP 2002537407	W		JP 2000-601138	20000223	<--
			WO 2000-US4657	20000223	<--
US 6713057	B1	Provisional	US 1999-121447P	19990224	<--
			US 2000-511532	20000223	<--
AU 776785	B2		AU 2000-32429	20000223	<--
US 2005079998	A1	Provisional	US 1999-121447P	19990224	<--
		Cont of	US 2000-511532	20000223	<--
			US 2003-640502	20030813	
EP 1155121	B1		EP 2000-910316	20000223	<--
			WO 2000-US4657	20000223	<--
DE 60027551	E		DE 2000-00027551	20000223	<--
			EP 2000-910316	20000223	<--
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FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000032429	A	Based on	WO 2000050574
EP 1155121	A1	Based on	WO 2000050574
JP 2002537407	W	Based on	WO 2000050574
AU 776785	B2	Previous Publ.	AU 2000032429
		Based on	WO 2000050574
US 2005079998	A1	Cont of	US 6713057
EP 1155121	B1	Based on	WO 2000050574
DE 60027551	E	Based on	EP 1155121
		Based on	WO 2000050574

PRIORITY APPLN. INFO: **US 1999-121447P 19990224; US 2000-511532 20000223;** US 2003-640502 20030813

INT. PATENT CLASSIF.:

MAIN: A61K031-164; A61K038-00; A61K038-46; A61K045-00; **C12N009-00**

SECONDARY: A01N043-04; A01N061-00; A61K009-127; A61K031-21; A61K031-22; A61K031-235; A61K031-351; A61K031-366; A61K031-40; A61K031-401; A61K031-403; A61K031-4045; A61K031-405; A61K031-685; A61K038-28; A61K045-06; A61K047-48; **A61P001-16; A61P003-00;**

A61P003-04; **A61P003-06**;
A61P009-10; **A61P031-12**;
A61P037-06; **A61P043-00**;
C12N009-50; C12N015-09; C12Q001-02; C12Q001-44;
C12Q001-68; G01N033-92

BASIC ABSTRACT:

WO 200050574 A UPAB: 20001023

NOVELTY - An anti-lipemic drug (I) comprising at least 1 effector of sterol regulatory element binding protein-1 (SREBP-1), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a method (II) for detecting an effector of SREBP-1 or LDL (low density lipoprotein) receptor biosynthesis, comprising contacting a population of cells capable of expressing SREBP-1 with a candidate effector to induce maturation of the SREBP-1, culturing the cells in medium and detecting maturation of SREBP-1 or biosynthesis of the LDL receptor;

(2) a method (III) for determining therapeutic capacity of an effector of SREBP-1 or (I) for treating a cholesterol related disease in a mammal comprising (II); and

(3) a method (IV) for determining therapeutic capacity of (I) in a Watanabe heritable hyperlipidemic rabbit or apolipoprotein E negative mouse comprising administering (I) to the rabbit or mouse to reduce cholesterol levels to 10-20%, and detecting the serum cholesterol reduction in the rabbit or mouse.

ACTIVITY - Antilipemic; **cerebroprotective**; anorectic; antiarteriosclerotic; hepatotropic; neuroprotective; antiinflammatory; immunosuppressive; **cardioactive.**

No relevant biological data is given.

MECHANISM OF ACTION - Modulator of serum cholesterol level, SREBP-1 level, LDL receptor level, fatty acid synthesis, and amyloid precursor protein production (claimed).

USE - (I) is useful for modulating serum cholesterol level, SREBP-1 level, LDL receptor level, fatty acid synthesis and production of amyloid precursor protein (beta APP) in a mammal for the treatment of hyperlipoproteinemia including hypercholesterolemia, **stroke**, obesity, **cardiac** disease, including atherosclerosis, **cerebral** atherosclerosis, cholesterol ester storage disorder, liver disease, including organ transplantation failure and cirrhosis, diseases of the biliary system or viral infection facilitating encephalitis. (I) is useful for treating disorders associated with high serum cholesterol levels in a mammal (claimed).

ADVANTAGE - (I) exhibits an ID50 of 20-90% as determined in a standard in vitro HMG (high mobility group protein) CoA (coenzyme A) reductase assay. (I) provides dual anti-cholesterol activity, by increasing LDL (low density lipoprotein) receptor activity, particularly by enhancing LDL receptor levels and by reducing serum cholesterol. (I) has better activity and can be administered at lower dosages than conventional agents. Patient tolerance of (I) is also positively impacted.

Dwg.0/15

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B04-E03E; B04-H08; B04-L01; B04-M01; B04-N02; B11-C08E; B12-K04A; B14-E12; **B14-F01**; **B14-F06**; **B14-F07**; B14-G02C; B14-N12; B14-N16; D05-H09; D05-H12A; D05-H17A

TECH UPTX: 20001023

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Drug: (I) is sufficient to reduce serum cholesterol level in a mammal by at least 20% when compared to a suitable control mammal, as determined by a standard serum

cholesterol binding assay. (I) comprises at least 1 synthetic or semi-synthetic inhibitor of HMG (high mobility group protein) CoA (coenzyme A) reductase or HMG CoA synthetase and at least 1 caspase, cpp32 protease (caspase-3). The inhibitor is a drug such as fluvastatin, simvastatin, lovastatin, pravastatin, mevinolin (compactin) or atorvastatin. The SREBP-1 effector is a **sphingolipid**, tumor necrosis factor (TNF-alpha), neutral **sphingomyelinase** (N-**SMase**) or a therapeutically effective fragment or cholesterol. N-**SMase** is encoded by a sequence (or its complement) having at least 70% sequence identity to a fully defined sequence of 1197 base pairs (bp) given in the specification. The **sphingolipid** is a naturally occurring **ceramide** or C-2,4,6 or 8 **ceramide** and is covalently linked to one of the inhibitors. The hydroxyl group on the **inhibitor** is covalently linked to the group of the **ceramide.** The N-**SMase** or fragment is covalently linked to one of the **inhibitors.** (I) comprises (covalently linked in sequence), **ceramide** or N-**SMase**, a heterobifunctional spacer group linked to the C-3 group of the **ceramide** or amide group of the N-**SMase**, and the hydroyxl (-OH) group of the fluvastatin, simvastatin, lovastatin, pravastatin, mevinolin (compactin) or atorvastatin, or derivative linked to a reactive carbon atom on the heterobifunctional spacer. (I) is specifically formulated for topical or related use and comprises components sufficient to provide (I) as a liposome formulation, which is specifically adapted for hepatic administration.

Preferred Method: In (II), (III) and (IV) the cells are further capable of responding to an increase or decrease in intracellular **ceramide** level. (II) and (III) further comprises monitoring LDL receptor activity. The candidate agent is N-**SMase**, **sphingomyelin**, **ceramide**, cpp 32 or cholesterol.

ABEX UPTX: 20001023

SPECIFIC SEQUENCES - N-**SMase** comprises 862-1414 nucleotides of a fully defined sequence of 1197 bp (given in the specification).

ADMINISTRATION - (I) is administered orally, intramuscularly, intraperitoneally, via a **stent** or related implementation, topically (including transdermal, buccal or sublingual) or nasally at a dose of 0.01-100 mg/kg of body weight of patient per day, preferably 1-20 mg/kg/day.

EXAMPLE - No relevant examples are given.

L161 ANSWER 39 OF 127 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-387802 [33] WPIX
DOC. NO. CPI: C2000-117806
TITLE: Novel method for identifying inhibitors of fungal inositolphosphoryl-**ceramide** (IPC) synthase, used for identifying antifungal agents.
DERWENT CLASS: B04 C07 D16
INVENTOR(S): CHAVDA, J S; SCHNELL, N F; CHAVADA, J S
PATENT ASSIGNEE(S): (ASTR) ASTRAZENECA UK LTD; (ASTR) ASTRAZENECA AB
COUNTRY COUNT: 91
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2000029590	A1	20000525	(200033)*	EN	15	C12N015-81<--

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES

FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS
LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL
TJ TM TR TT UA UG US UZ VN YU ZA ZW

AU 2000010661	A	20000605	(200042)		C12N015-81<--
EP 1131449	A1	20010912	(200155)	EN	C12N015-81
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
JP 2002530084	W	20020917	(200276)	17	C12N015-09
US 6808892	B1	20041026	(200470)		C12Q001-18

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE	
WO 2000029590	A1	WO 1999-GB3789	19991112	<--
AU 2000010661	A	AU 2000-10661	19991112	<--
EP 1131449	A1	EP 1999-954249	19991112	<--
		WO 1999-GB3789	19991112	<--
JP 2002530084	W	WO 1999-GB3789	19991112	<--
		JP 2000-582572	19991112	<--
US 6808892	B1	WO 1999-GB3789	19991112	<--
		US 2001-831290	20010508	

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000010661	A	Based on	WO 2000029590
EP 1131449	A1	Based on	WO 2000029590
JP 2002530084	W	Based on	WO 2000029590
US 6808892	B1	Based on	WO 2000029590

PRIORITY APPLN. INFO: **GB 1998-25055**
19981117

INT. PATENT CLASSIF.:

MAIN:	C12N015-09; C12N015-81; C12Q001-18
SECONDARY:	A61K045-00; **A61P031-10**; **A61P043-00**; C12N001-15; C12N001-19; **C12N009-99**; C12Q001-02; C12Q001-25; G01N033-15; G01N033-50
INDEX:	C12N001-19; C12R001:865

BASIC ABSTRACT:

WO 200029590 A UPAB: 20000712

NOVELTY - A novel method for identifying inhibitors of fungal inositolphosphoryl-**ceramide** (IPC) synthase.

DETAILED DESCRIPTION - The method comprises:

(a) contacting a test compound with engineered cells whose capability to synthesize **sphingolipids** depends in the addition of exogenous **phytosphingosine** and which are capable of sustained growth via compensatory phospholipids;

(b) adding **phytosphingosine**; and

(c) determining IPC synthase inhibition by the test compound by reference to any cell growth inhibition.

INDEPENDENT CLAIMS are also included for the following:

(1) engineered cells whose capability to synthesize **sphingolipids** depends in the addition of exogenous **phytosphingosine** and which are capable of sustained growth via compensatory phospholipids;

Saccharomyces cerevisiae (lcb1/pGPD-SLC-1); and

(2) a selective IPC synthase inhibitor identified using the method of the invention.

USE - The method and cells are used for identifying inhibitors of fungal inositolphosphoryl-**ceramide** (IPC) synthase. Such inhibitors are potent and selective antifungal agents.

ADVANTAGE - The present invention provides a simple assay for identifying inhibitors of inositolphosphoryl- **ceramide** (IPC) synthase, which is not as labor-intensive as prior art methods.

DESCRIPTION OF DRAWING(S) - The figure shows the **inhibition** of growth by aureobasidin A in strain lcb1::kanMX, pnS149 with added **phytosphingosine.**

Dwg.1a/1

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B04-B04M; B04-C01; B04-E03E; B04-F0100E; B04-F09C0E; B04-L07; B04-M01; B11-C08E1; B12-K04D; B14-A04; C04-B04M; C04-C01; C04-E03E; C04-F0100E; C04-F09C0E; C04-L07; C04-M01; C11-C08E1; C12-K04D; C14-A04; D05-C; D05-H09; D05-H12A; D05-H14A2

TECH UPTX: 20000712

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Cell: The host strain is an lcb1/SLC1-1 strain. Especially, the SLC-1 gene is under the control of the glyceraldehyde 3-phosphate dehydrogenase (GDP3) gene. Alternatively, the host strain is lcb1/pGPD-SLC- 1.

ABEX UPTX: 20000712

EXAMPLE - No relevant example given.

L161 ANSWER 40 OF 127 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-072612 [06] WPIX
DOC. NO. CPI: C2000-020792
TITLE: New **sphingosine** kinase, used to treat diseases involving abnormal cell proliferation, e.g. cancer.
DERWENT CLASS: B04 D16
INVENTOR(S): SPIEGEL, S
PATENT ASSIGNEE(S): (DEAN-N) OFFICE DEAN RES & GRADUATE EDUCATION; (SPIE-I) SPIEGEL S
COUNTRY COUNT: 23
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 9961581	A2	19991202	(200006)*	EN	115	C12N000-00<--
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE						
W: AU CA JP US						
AU 9940979	A	19991213	(200020)			C12N000-00<--
EP 1235913	A2	20020904	(200266)	EN		C12N015-54
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI NL PT SE						

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE	
WO 9961581	A2	WO 1999-US11521	19990525	<--
AU 9940979	A	AU 1999-40979	19990525	<--
EP 1235913	A2	EP 1999-924494	19990525	<--
		WO 1999-US11521	19990525	<--

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9940979	A	Based on	WO 9961581

EP 1235913 A2 Based on WO 9961581

PRIORITY APPLN. INFO: **US 1998-96049P 19980811; US 1998-86657P 19980526**

INT. PATENT CLASSIF.:
MAIN: C12N000-00; C12N015-54
SECONDARY: C07K016-40; **C12N009-12**; C12Q001-68; G01N033-577; G01N033-68

BASIC ABSTRACT:

WO 9961581 A UPAB: 20000203

NOVELTY - Isolated DNA (I) encoding a **sphingosine** kinase (II) or its fragments are new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) recombinant DNA construct containing a vector and (I);

(2) host cell transfected with this construct;

(3) recombinant production of (II) by culturing cells of (b);

(4) recombinant (II) produced this way;

(5) screening for agents or drugs that inhibit or promote activity of (II);

(6) detecting (II) in a sample by reaction with specific antibodies (Ab) or by polymerase chain reaction;

(7) Ab;

(8) agents or drugs (A) that inhibit or promote (II) activity;

(9) diagnostic kits for detecting (II)-related RNA or DNA, by hybridization and/or amplification;

(10) measuring **sphingosine**-1-phosphate (III);

(11) increasing (II) concentration in a cell by introducing (I);

(12) decreasing cell proliferation by reducing activity or expression of (II);

(13) reducing cell death by increasing activity or expression of (II); and

(14) treating diseases that involve increased cell proliferation or altered cell migration or motility using an agent that reduces or eliminates expression or function of (II).

ACTIVITY - Anticancer; antiproliferative; anti-atherosclerotic; antineurodegeneration.

MECHANISM OF ACTION - Expression of (II) in cells results in formation of **sphingosine**-1-phosphate (III), a known second messenger, and confers serum-independent growth; increases proliferation, and **suppresses** serum-deprivation or **ceramide**-induced apoptosis. When c-myc-labeled (II) was expressed transiently in NIH 3T3 cells, the proportion of cells in S phase was increased (and this effect was potentiated by serum or platelet-derived growth factor). Stable expression greatly increased cell growth in low-serum medium (up to a 7-fold increase in incorporation of tritiated thymidine).

USE - (I) is used:

(a) for recombinant production of (II);

(b) to increase (II) content of cells, specifically for reducing cell death and/or increasing cell proliferation; and

(c) to produce transfected cells that are used to screen for agents (A) that inhibit or promote (II) activity.

Fragments of (I) are used as primers and probes for detecting (I) by standard amplification and/or hybridization methods, also as sources of ribozymes and antisense oligonucleotides. (II) is used:

(A) in preparation and analysis of **sphingosine**-1-phosphate (III);

(B) to raise specific antibodies (Ab);

(C) in drug screening, and

(D) therapeutically against diseases involving abnormal cell death or proliferation.

(A) that reduce activity or expression of (II) are used:

(i) to reduce cell proliferation, specifically for treating cancer, and

(ii) to treat diseases associated with abnormal cell migration or motility, particularly cancer, restenosis or diabetic neuropathy (but also atherosclerosis, stroke and Alzheimer's disease).

(A) that stimulate (II) can be used to treat conditions associated with reduced cell proliferation, e.g. developmental retardation. Ab are used in immunoassays to determine (II); as therapeutic inhibitors, and , when labeled, for diagnosis and prognosis of cancer, e.g. to predict proliferative and metastatic potential of cancers.

ADVANTAGE - Recombinant (II) provides a method for quantifying sphingosine-1-phosphate that is more specific than known processes.

Dwg.0/7

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B04-C01; B04-E03E; B04-E08; B04-F0100E; B04-G01; B04-L0400E; B04-N02A; B11-C08E3; B11-C08E5; B12-K04; **B14-F02D1**; **B14-F07**; B14-H01B; B14-J01A; B14-N16; B14-S04; D05-H09; D05-H11; D05-H12A; D05-H12D1; D05-H12D2; D05-H12D4; D05-H12E; D05-H14; D05-H17A3; D05-H18B

TECH UPTX: 20000203

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Nucleic Acid: The nucleic acid is purified and contains at least 30 nucleotides from the sequences present in Genbank AF068748 or AF068749, encoding a peptide of murine (II), particularly a 381 amino acid sequence (given in the specification). Preferred Vectors: These are functional in prokaryotic or eukaryotic cells.

Preparation: (II) was isolated from rat kidney, digested with trypsin and several of the peptide fragments sequenced. These sequences were used to search databases of expressed sequence tags to identify holomogy with the closely related clones AA107451 and AA389187. Sequencing of the full-length cDNAs revealed open reading frames for 381 and 388 amino acid proteins, designated SPHK1a and SPHK1b, both of which contained calcium/calmodulin binding sites. Further database searches showed that homologous proteins were present in many different organisms. The nucleic acid can be expressed in any standard vector/host system.

TECHNOLOGY FOCUS - BIOLOGY - Preferred Methods: To identify (A) that inhibit (promote) (II) activity, a recombinant construct containing (I) is introduced into a cell which is then treated with one or more test compounds, and any inhibition (promotion) of activity determined by measuring (II)-dependent phosphorylation of cellular lipids, in comparison with that measured in untreated cells. To measure (III), this is first separted from other phospholipids in the sample (e.g. by extraction into an aqueous phase); converted to **sphingosine** (e.g. using alkaline phosphatase) and the product phosphorylated, in presence of (I), using a labeled form of phosphate. The assay can determine 25 fmole to 250 mumole of (III).

Preparation: Ab are produced by usual methods of immunization and cell fusion.

ABEX UPTX: 20000203

ADMINISTRATION - (I), its antagonists and other therapeutic agents, are administered topically, by injection, orally or from a biodegradable implant. Typically the dose is 1 pg to 10 mg/kg.

L161 ANSWER 41 OF 127 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN

ACCESSION NUMBER: 1999-263700 [22] WPIX
CROSS REFERENCE: 2003-605464 [57]; 2003-663394 [62]
DOC. NO. NON-CPI: N1999-196410
DOC. NO. CPI: C1999-077758
TITLE: **Sphingosine**-1-phosphate lyase, polynucleotides and **modulators.**
DERWENT CLASS: B04 D16 P14 S03
INVENTOR(S): SABA, J D; ZHOU, J; FYRST, H
PATENT ASSIGNEE(S): (CHIL-N) CHILDREN'S HOSPITAL OAKLAND RES INST; (CHIL-N) CHILDREN'S HOSPITAL MEDICAL CENT; (CHIL-N) CHILDRENS HOSPITAL & RES CENT AT OAKLAND; (CHIL-N) CHILDREN'S HOSPITAL RES CENT AT OAKLAND
COUNTRY COUNT: 83
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 9916888	A2	19990408	(199922)*	EN	97	C12N015-60<--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW						
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW						
AU 9897794	A	19990423	(199935)			C12N015-60<--
EP 1027443	A2	20000816	(200040)	EN		C12N015-60<--
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE						
JP 2001518303	W	20011016	(200176)		101	C12N015-09
US 6423527	B1	20020723	(200254)			C12N009-88<--
US 6495359	B1	20021217	(200307)			C12N009-88<--
US 2003059922	A1	20030327	(200325)			G01N033-574
US 2003166897	A1	20030904	(200359)			C07H021-02
US 2005221346	A1	20051006	(200566)			C12Q001-68
US 7041291	B2	20060509	(200632)			A61K039-00

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE	
WO 9916888	A2		WO 1998-US20365	19980929	<--
AU 9897794	A		AU 1998-97794	19980929	<--
EP 1027443	A2		EP 1998-951982	19980929	<--
			WO 1998-US20365	19980929	<--
JP 2001518303	W		WO 1998-US20365	19980929	<--
			JP 2000-513957	19980929	<--
US 6423527	B1		US 1997-939309	19970929	<--
US 6495359	B1	Div ex	US 1997-939309	19970929	<--
			US 2001-849180	20010504	
US 2003059922	A1	Div ex	US 1997-939309	19970929	<--
		Cont of	US 2001-849180	20010504	
			US 2002-286175	20021030	
US 2003166897	A1	Div ex	US 1997-939309	19970929	<--
			US 2002-197073	20020715	
US 2005221346	A1	CIP of	US 1997-939309	19970929	<--
		CIP of	US 1999-356643	19990719	<--
		Cont of	US 2002-53510	20020117	
			US 2004-979085	20041101	
US 7041291	B2	Div ex	US 1997-939309	19970929	<--
			US 2002-197073	20020715	

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9897794	A Based on	WO 9916888
EP 1027443	A2 Based on	WO 9916888
JP 2001518303	W Based on	WO 9916888
US 6495359	B1 Div ex	US 6423527
US 2003059922	A1 Div ex	US 6423527
	Cont of	US 6495359
US 2003166897	A1 Div ex	US 6423527
US 2005221346	A1 CIP of	US 6423527
	CIP of	US 6569666
	Cont of	US 6830881
US 7041291	B2 Div ex	US 6423527

PRIORITY APPLN. INFO: **US 1997-939309**
19970929; US 2001-849180
20010504; US 2002-286175
20021030; US 2002-197073
20020715; **US 1999-356643**
19990719; US 2002-53510
20020117; US 2004-979085
20041101

INT. PATENT CLASSIF.:
MAIN: A61K039-00; C07H021-02; **C12N009-88**; C12N015-09; C12N015-60; C12Q001-68; G01N033-574
SECONDARY: A01K067-027; A61K031-711; A61K038-51; A61K039-395; A61K045-00; A61K048-00; **A61P035-00**; **A61P043-00**; C07H021-04; C07K016-40; C12N001-21; C12N005-00; C12N005-06; C12N005-10; C12N015-00; C12P021-02; G01N033-15; G01N033-50; G01N033-68

BASIC ABSTRACT:

WO 9916888 A UPAB: 20060518

NOVELTY - **Sphingosine**-1-phosphate lyase (SPL) polynucleotides are new.

DETAILED DESCRIPTION - An isolated polynucleotide comprising a sequence chosen from:

(a) one of two 1707 bp sequences (human and murine; both given in the specification);

(b) nucleotide sequences encoding SPL active polypeptides, that hybridize to the complements of (a) under moderately stringent conditions; and

(c) nucleotide sequences that encode a polypeptide encoded by any of (a) or (b).

INDEPENDENT CLAIMS are also included for:

(1) polynucleotides encoding murine and human SPL of 568 amino acids (sequences given in the specification), or variants that have SPL activity;

(2) a recombinant expression vector comprising a polynucleotide as above;

(3) a host cell transformed or transfected with an expression vector as in (2);

(4) an isolated polynucleotide comprising at least 100 nucleotides complementary to the human or murine 1707 bp sequences;

(5) preparation of an SPL;

(6) a polypeptide comprising human or murine SPL or a variant with SPL activity or encoded by polynucleotides as above;

(7) identifying agents that modulate SPL activity;

(8) an isolated (monoclonal) antibody that binds to the human or

murine SPL or a 542 amino acid sequence;
(9) detection of SPL;
(10) a transgenic animal in which SPL activity is reduced compared to a wild-type animal; and
(11) a cell line derived from the transgenic animal of (10).
ACTIVITY - Cytostatic.
MECHANISM OF ACTION - **Sphingosine**-1-phosphate lyase **inhibitor.**
USE - Using an SPL inhibitor can inhibit growth of cancer cells, especially breast cancer cells (claimed). The inhibitor (polynucleotides preventing expression of SPL genes, or antibodies against SPL) can also be used to prevent development and/or metastasis of cancer, especially where the inhibitor is linked to an ant tumor or anti estrogen receptor antibody (claimed). Cancer can be diagnosed by detection of alterations in SPL genes, especially in breast tumor biopsies (claimed).
Cancer prognosis can be evaluated by looking for alterations in the SPL genes, especially where the alteration is a deletion of residues 354-433 of the 568 amino acid SPL sequence. Antibodies can also be used to diagnose cancer (claimed).
ADVANTAGE - **Inhibition** of SPL **prevents** degradation of **sphingosine**-1-phosphate, an endogenous tumor **suppressor** lipid that potently **inhibits** breast cancer cell growth and invasiveness, while not affecting the growth of non-tumor cells.
Dwg.0/8

FILE SEGMENT: CPI EPI GMPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B04-C01G; B04-E03F; B04-E08; B04-F0100E; B04-G03; B04-G21; B04-P0100E; B11-C07A; B12-K04A1; B12-K04F; B14-H01; D05-H09; D05-H11; D05-H12A; D05-H12E; D05-H14; D05-H16A; D05-H17A3
EPI: S03-E14H

TECH UPTX: 19990609
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Methods: The SPL can be one of the 568,568 542 or 589 amino acid sequences given in the specification. SPL modulators can be identified by first contacting a candidate agent with cells that express SPL or with a human, murine, C. elegans or Saccharomyces cerevisiae SPL polypeptide. Secondly the level of SPL or mRNA encoding SPL is measured in the cells, relative to a predetermined level in the absence of the agent. Alternatively the ability of the SPL to degrade SP is measured relative to an ability in the absence of the candidate agent. Candidate agents can then be identified.
Preferred Modulators: Endogenous expression of SPL is inhibited by antisense polynucleotides. Antibodies (or antigen-binding fragments) inhibit the ability of the SPL to degrade SP.

ABEX UPTX: 19990609
WIDER DISCLOSURE - WIDER DESCRIPTION - Saccharomyces cerevisiae and C. elegans **sphingosine**-1-phosphate lyases having a 589 and 542 amino acid sequence, respectively are disclosed. The yeast SPL is encoded by the bst1 (bestower of **sphingosine** tolerance) gene (1770 bp) and the C. elegans SPL is encoded by a 1629 bp sequence. An altered human SPL gene of 1467 bp found in human **brain** tumor cells and its product of 488 amino acids are disclosed. The mutant SPL comprises a deletion of residues 354-433 of the normal SPL.

EXAMPLE - In order to determine whether the murine SPL gene was able to restore biochemical SPL activity to a bst1DELTA strain, an untransformed bst1DELTA strain and a bst1DELTA strain transformed with pYES2 containing either BST1 or the putative murine SPL gene, were grown to exponential phase (A600=1.0) in either minimal or uracil medium containing galactose

as a carbon source. Whole cell extracts were prepared from each strain as described above, adjusted for protein concentration, and evaluated for SPL activity, using 3H-**dihydrosphingosine**-1-phosphate. Qualitative analysis of product was performed by autoradiography. Quantitative measurement was performed by scraping TLC plates and determining radioactivity present using a standard scintillation counter. Results showed that expression of both the yeast and mouse sequences restored SPL activity to the bst1DELTA strain, vector alone had no effect, confirming the identity of the mouse sequence as SPL.

L161 ANSWER 42 OF 127 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1999-214617 [18] WPIX
DOC. NO. NON-CPI: N1999-157958
DOC. NO. CPI: C1999-063228
TITLE: Treatment of conditions associated with an extracellular zinc **sphingomyelinase** by administration of a zinc **sphingomyelinase inhibitor.**
DERWENT CLASS: B04 D16 S03
INVENTOR(S): SCHISSEL, S L; TABAS, I; WILLIAMS, K J
PATENT ASSIGNEE(S): (UYCO) UNIV COLUMBIA NEW YORK; (SCHI-I) SCHISSEL S L; (TABA-I) TABAS I; (WILL-I) WILLIAMS K J; (UYJE-N) UNIV JEFFERSON THOMAS
COUNTRY COUNT: 83
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 9911283	A1	19990311	(199918)*	EN	189	A61K038-46<--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW						
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW						
AU 9893016	A	19990322	(199931)			<--
US 5989803	A	19991123	(200002)			C12Q001-00<--
EP 1009426	A1	20000621	(200033)	EN		A61K038-46<--
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE						
JP 2001514232	W	20010911	(200167)		187	A61K045-00
US 2003026796	A1	20030206	(200313)			A61K038-43
US 6613322	B2	20030902	(200359)			A61K038-46
US 2004047851	A1	20040311	(200419)			A01N059-00

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE	
WO 9911283	A1		WO 1998-US18362	19980904	<--
AU 9893016	A		AU 1998-93016	19980904	<--
US 5989803	A		US 1997-937234	19970905	<--
EP 1009426	A1		EP 1998-945870	19980904	<--
			WO 1998-US18362	19980904	<--
JP 2001514232	W		WO 1998-US18362	19980904	<--
			JP 2000-508385	19980904	<--
US 2003026796	A1	CIP of	US 1997-937234	19970905	<--
		Cont of	WO 1998-US18362	19980904	<--
			US 2000-518805	20000303	<--
US 6613322	B2	CIP of	US 1997-937234	19970905	<--
		Cont of	WO 1998-US18362	19980904	<--
			US 2000-518805	20000303	<--

US 2004047851	A1	CIP of	US 1997-937234	19970905	<--
		Cont of	WO 1998-US18362	19980904	<--
		Cont of	US 2000-518805	20000303	<--
			US 2003-646412	20030822	

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9893016	A	Based on	WO 9911283
EP 1009426	A1	Based on	WO 9911283
JP 2001514232	W	Based on	WO 9911283
US 6613322	B2	CIP of	US 5989803
US 2004047851	A1	CIP of	US 5989803
		Cont of	US 6613322

PRIORITY APPLN. INFO: **US 1997-937234 19970905; US 2000-518805 20000303;** US 2003-646412 20030822

INT. PATENT CLASSIF.:

MAIN: A01N059-00; A61K038-43; A61K038-46; A61K045-00; C12Q001-00

SECONDARY: A61K031-711; A61K038-00; A61K038-48; A61K038-54; A61K039-395; A61K048-00; **A61P001-16**; **A61P009-10**; **A61P025-00**; **A61P029-00**; **A61P031-00**; **A61P031-12**; **A61P037-00**; **A61P043-00**; C07K002-00; C07K016-40; **C12N009-14**; C12N015-02; C12Q001-34; C12Q001-66; G01N033-53

ADDITIONAL: C07H021-00

BASIC ABSTRACT:

WO 9911283 A UPAB: 20000725

NOVELTY - New treatment of a condition associated with an extracellular zinc **sphingomyelinase** (ZS) activity comprises administration of a ZS **inhibitor** to decrease extracellular ZS activity.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for:

(1) determining whether a compound inhibits an activity of an extracellular ZS involving **ceramide** formation comprising:

(a) contacting a sample containing the ZS under acidic pH conditions with a substrate of the ZS enzyme and the test compound;

(b) measuring the concentration of **ceramide** in the sample;

(c) determining the amount of ZS activity on the sample based on the **ceramide** concentration, and

(d) comparing the amount of ZS activity determined with that obtained in the absence of test compound;

(2) screening a library of compounds for ZS inhibitory activity;

(3) determining whether a subject is at increased risk for becoming afflicted with an increase in the concentration of extra cellular ZS activity; and

(4) determining whether a subject has lipoproteins susceptible to extra cellular ZS activity and is at increased risk for becoming afflicted with a condition associated with extracellular ZS activity.

USE - Conditions which can be treated include atherosclerotic **vascular** disease (e.g. **coronary artery** disease, **cerebral** or peripheral **vascular** diseases), inflammatory disease, infectious disease, autoimmune disease and demyelinating disease (e.g. multiple sclerosis, progressive multifocal leucoencephalopathy, Guillain Barre syndrome, Retrobulbar neuritis, acute

rubella encephalitis, chronic relapsing polyneuropathy, intravascular lymphomatosis, Krabbe disease, globoid cell leukodystrophy, subacute combined degeneration of the spinal cord and **brain**, allergic encephalitis, murine caronavirus, hepatitis virus infection or Theiler's murine encephalomyelitis).

ADVANTAGE - None given.

Dwg.0/26

FILE SEGMENT: CPI EPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B04-B04B1; B04-B04G; B04-B04L; B04-C01; B04-E01; B04-G01; B04-L01; B04-N02; B12-K04A1; B14-A02A5; B14-A02B; B14-C03; **B14-F07**; B14-G02D; B14-G03; D05-H09
EPI: S03-E14H1; S03-E14H6

TECH UPTX: 19990503

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Inhibitors: The inhibitor is a peptide or polypeptide, a peptidomimetic compound, an organic compound, a nucleic acid, an inorganic compound, or an antibody or fragment (e.g. an antibody capable of binding to and inactivating ZS, or an antibody comprising a monoclonal or polyclonal antibody), a compound capable of competing with **sphingomyelin** for bonding to naturally occurring ZS, or a pseudoenzyme. The **inhibitor** may comprise a portion of a naturally occurring ZS, consisting of a **sphingomyelin** binding site of the sphinogomyelinase.

Preferred Method: To determine whether a subject is at increased risk for becoming afflicted with an increase in the concentration of extracellular ZS activity, extracellular ZS activity is determined in a sample of body fluid (plasma, blood, serum, interstitial fluid, **cerebrospinal** fluid, joint fluid, tears, semen, urine, saliva, bile, amniotic fluid) and compared with previously obtained values.

ABEX UPTX: 19990503

ADMINSTRATION - Administration may be intralesional, intraperitoneal, by intramuscular or intravenous injection, by infusion, liposome-mediated delivery, topical, nasal, oral, anal, subcutaneous, vaginal, sublingual, intrathecal, uretheral, transdermal, ocular or otic.

EXAMPLE - No relevant example.

L161 ANSWER 43 OF 127 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1998-377673 [32] WPIX
DOC. NO. CPI: C1998-114785
TITLE: Human neutral **sphingomyelinase** - used to, e.g. treat N-**Smase** associated disorders, e.g. Crohn's disease, obesity, diabetes, and Alzheimer's disease.
DERWENT CLASS: B04 D16
INVENTOR(S): CHATTERJEE, S
PATENT ASSIGNEE(S): (UYJO) UNIV JOHNS HOPKINS; (UYJO) UNIV JOHNS HOPKINS SCHOOL MEDICINE; (CHAT-I) CHATTERJEE S
COUNTRY COUNT: 82
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 9828445	A1	19980702	(199832)*	EN	47	C12Q001-68<--

RW: AT BE CH DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG

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        US UZ VN YU ZW
AU 9858093      A  19980717 (199848)          C12Q001-68<--
US 5919687      A  19990706 (199933)          C12N009-22<--
EP 948651       A1 19991013 (199947)  EN      C12Q001-68<--
    R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
JP 2001507575   W  20010612 (200139)       53 C12N015-09
AU 747090       B  20020509 (200238)          C12Q001-68
US 2002160484   A1 20021031 (200274)          C12N009-16<--
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APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE	
WO 9828445	A1	WO 1997-US24051	19971223	<--
AU 9858093	A	AU 1998-58093	19971223	<--
US 5919687	A	US 1996-774104	19961224	<--
EP 948651	A1	EP 1997-954272	19971223	<--
		WO 1997-US24051	19971223	<--
JP 2001507575	W	WO 1997-US24051	19971223	<--
		JP 1998-529095	19971223	<--
AU 747090	B	AU 1998-58093	19971223	<--
US 2002160484	A1 Div ex	US 1996-774104	19961224	<--
		US 1999-282879	19990331	<--

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9858093	A	Based on	WO 9828445
EP 948651	A1	Based on	WO 9828445
JP 2001507575	W	Based on	WO 9828445
AU 747090	B	Previous Publ.	AU 9858093
		Based on	WO 9828445

PRIORITY APPLN. INFO: **US 1996-774104 19961224; US 1999-282879 19990331**

INT. PATENT CLASSIF.:

MAIN: **C12N009-16**; **C12N009-22**; C12N015-09; C12Q001-68

SECONDARY: A01N001-02; A61K038-00; A61K038-46; A61K039-395; **A61P003-00**; **A61P029-00**; **A61P035-00**; **A61P043-00**; C07H021-04; C12N001-14; C12N001-20; C12N001-21; C12N005-00; **C12N009-20**; C12N015-00; C12Q001-34

BASIC ABSTRACT:

WO 9828445 A UPAB: 19991122

An isolated nucleic acid (I) encoding human neutral **sphingomyelinase** (N-**Smase**), is new. Also claimed are: (1) a recombinant vector comprising (I); (2) a host cell comprising the vector of (1); (3) a nucleic acid that hybridises to the 1197 bp cDNA sequence given in the specification; (4) an isolated N-**Smase** having an apparent molecular weight of about 44 kDa as determined by PAGE using sodium laurylsarocine; (5) an isolated polypeptide having at least 70% sequence identity to the 397 amino acid sequence given in the specification, and (6) a storage sample of sperm or seminal fluid comprising the sperm or seminal fluid and a storage effective amount of a fragment or derivative of N-**Smase**.

USE - The host cell of (2) can be used to produce N-**Smase**.

N-**Smase** can be used in a method for identifying a compound

useful in the diagnosis or treatment of a human neutral **sphingomyelinase** related disorder. N-**Smase**, and (I) can be used for **modulating** N-**Smase** activity, and for treating a disorder associated with N-**Smase**. The N-**Smase** disorders that can be treated with (I) or N-**Smase**, is an inflammatory disorder, arthritis, osteoarthritis, Crohn's disease, obesity, diabetes, cirrhosis, susceptible tumours, central nervous system disorder, **vascular restenosis**, **arterial** occlusion arising from plaque formation, **cardiac** disease where LV dysfunction occurs, hypercholesterolaemia, cholesteryl ester storage disorder, renal failure, HIV infection, **depression**, schizophrenia, neurodegeneration, and Alzheimer's disease. An antibody against N-**Smase** can be used to **reduce** tumour necrosis factor alpha (TNF- alpha) **induced** apoptosis of mammalian cells (all claimed).

Dwg.0/8

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB
MANUAL CODES: CPI: B04-C01; B04-E01; B04-E02E; B04-E08; B04-F03; B04-L05; B14-E12; **B14-F09**; B14-J01B3; D05-H09; D05-H11; D05-H12A; D05-H12E; D05-H14; D05-H17A3

L161 ANSWER 44 OF 127 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1998-312142 [27] WPIX
DOC. NO. CPI: C1998-096255
TITLE: Use of **sphingomyelinase** in dermatological or cosmetic compositions - increases the level of skin and mucosal **ceramide**(s).
DERWENT CLASS: B04 D16 D21
INVENTOR(S): CAVALIERE, W V R; DE SIMONE, C; VESELY, R M A C; CAVALIERE, R M A; DE VESELY, R M A C V; CAVALIERE VESELY, R M A; CAVALIERE WIDOW VESELY, R M A
PATENT ASSIGNEE(S): (DSIM-I) DE SIMONE C; (CAVA-I) CAVALIERE R M A; (VSLP-N) VSL PHARMA LTD; (VSLP-N) VSL PHARM INC
COUNTRY COUNT: 70
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 9822082	A1	19980528	(199827)*	EN	16	A61K007-48<--
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW						
W: AL AU BA BB BG BR CA CN CU CZ EE GE GH HU IL IS JP KE KP KR LC LK LR LS LT LV MG MK MN MW MX NO NZ PL RO SD SG SI SK SL TR TT UA UG US UZ VN YU ZW						
AU 9851340	A	19980610	(199843)			A61K007-48<--
EP 941056	A1	19990915	(199942)	EN		A61K007-48<--
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE						
BR 9713287	A	19991026	(200009)			A61K007-48<--
CN 1240345	A	20000105	(200021)			A61K007-48<--
KR 2000057210	A	20000915	(200122)			A61K007-48<--
MX 9904749	A1	20000401	(200124)			A61K007-48<--
AU 732203	B	20010412	(200128)			A61K007-48
JP 2001505201	W	20010417	(200128)		17	A61K038-43
US 6258355	B1	20010710	(200141)			A01N063-00
IT 1296148	B	19990609	(200159)			A61K000-00<--
EP 941056	B1	20020612	(200239)	EN		A61K007-48
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE						
DE 69713379	E	20020718	(200255)			A61K007-48

ES 2176795	T3 20021201 (200305)		A61K007-48
US 2003077269	A1 20030424 (200330)		A61K038-46
US 2003086917	A1 20030508 (200337)		A61K038-46
US 6582695	B2 20030624 (200343)		A01N063-00
IL 130037	A 20040601 (200442)		A61K007-48
MX 216017	B 20030826 (200464)		A61K038-46
US 6962697	B2 20051108 (200573)		A01N063-00
US 2005265986	A1 20051201 (200579)		A61K038-46
US 39118	E 20060606 (200638)		A01N063-00

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE	
WO 9822082	A1	WO 1997-IT278	19971114	<--
AU 9851340	A	AU 1998-51340	19971114	<--
EP 941056	A1	EP 1997-946038	19971114	<--
		WO 1997-IT278	19971114	<--
BR 9713287	A	BR 1997-13287	19971114	<--
		WO 1997-IT278	19971114	<--
CN 1240345	A	CN 1997-180647	19971114	<--
KR 2000057210	A	WO 1997-IT278	19971114	<--
		KR 1999-704543	19990521	<--
MX 9904749	A1	MX 1999-4749	19990521	<--
AU 732203	B	AU 1998-51340	19971114	<--
JP 2001505201	W	WO 1997-IT278	19971114	<--
		JP 1998-523431	19971114	<--
US 6258355	B1	WO 1997-IT278	19971114	<--
		US 1999-308366	19990518	<--
IT 1296148	B	IT 1996-RM799	19961122	<--
EP 941056	B1	EP 1997-946038	19971114	<--
		WO 1997-IT278	19971114	<--
DE 69713379	E	DE 1997-613379	19971114	<--
		EP 1997-946038	19971114	<--
		WO 1997-IT278	19971114	<--
ES 2176795	T3	EP 1997-946038	19971114	<--
US 2003077269	A1 Div ex	US 1999-308366	19990518	<--
		US 2001-861774	20010522	
US 2003086917	A1 Div ex	US 1999-308366	19990518	<--
	Div ex	US 2001-861774	20010522	
		US 2002-307935	20021203	
US 6582695	B2 Div ex	US 1999-308366	19990518	<--
		US 2001-861774	20010522	
IL 130037	A	IL 1997-130037	19971114	<--
MX 216017	B	WO 1997-IT278	19971114	<--
		MX 1999-4749	19990521	<--
US 6962697	B2 Div ex	US 1999-308366	19990518	<--
	Div ex	US 2001-861774	20010522	
		US 2002-307935	20021203	
US 2005265986	A1 Div ex	US 1999-308366	19990518	<--
	Div ex	US 2001-861774	20010522	
	Div ex	US 2002-307935	20021203	
		US 2005-195673	20050803	
US 39118	E	WO 1997-IT278	19971114	<--
		US 1999-202579	19990518	<--
		US 1999-308366	19990518	<--

FILING DETAILS:

PATENT NO	KIND	PATENT NO

AU 9851340	A	Based on	WO 9822082
EP 941056	A1	Based on	WO 9822082
BR 9713287	A	Based on	WO 9822082
KR 2000057210	A	Based on	WO 9822082
AU 732203	B	Previous Publ.	AU 9851340
		Based on	WO 9822082
JP 2001505201	W	Based on	WO 9822082
US 6258355	B1	Based on	WO 9822082
EP 941056	B1	Based on	WO 9822082
DE 69713379	E	Based on	EP 941056
		Based on	WO 9822082
ES 2176795	T3	Based on	EP 941056
US 2003077269	A1	Div ex	US 6258355
US 2003086917	A1	Div ex	US 6258355
US 6582695	B2	Div ex	US 6258355
IL 130037	A	Based on	WO 9822082
MX 216017	B	Based on	WO 9822082
US 6962697	B2	Div ex	US 6258355
		Div ex	US 6582695
US 2005265986	A1	Div ex	US 6258355
		Div ex	US 6582695
US 39118	E	Reissue of	US 6258355
		Based on	WO 9822082

PRIORITY APPLN. INFO: **IT 1996-RM799**
19961122

INT. PATENT CLASSIF.:
MAIN: A01N063-00; A61K000-00; A61K007-48; A61K038-43; A61K038-46
SECONDARY: A01N063-02; A61K038-48; **A61P017-00**; C12N001-21; **C12N009-20**; C12P021-02

BASIC ABSTRACT:

WO 9822082 A UPAB: 19980709

Use of **sphingomyelinase** (I) for producing dermatological and/or cosmetic compositions suitable to be topically applied, to increase the levels of skin and mucosal **ceramides.** Also claimed is a dermatological or cosmetic composition which comprises an amount of (I) effective for increasing the level of skin and mucosal **ceramides**

.

(I) is obtained from Gram-positive or Gram-negative bacteria and/or lactic bacteria. Specified lactic bacteria are Lactobacillus acidophilus, L. brevis, L. buchneri, L. casei, L. catenaforme, L. cellobiosus, L. crispatus, L. curvatus, L. delbrueckii, L. fermentum, Streptococcus lactis, S. raffinolactis and S. thermophilus, etc. (I) is in the form of lyophilised or sonicated cells; and the composition contains 1x1012-1x1015 lactic bacteria/g. The composition may also contain e.g. exogenous **ceramide** or products containing it, **sphingomyelines**, fatty acids, cholesterol, **ceramidase inhibitors**, protease **inhibitors**, immunomodulators, vitamins, growth factors, surfactants, emulsifiers, stabilisers, etc.

USE - The composition may be topically applied to prevent or treat e.g. atopic eczema, dermatosis and dermatitis, especially atopic dermatitis, psoriasis, ichthyosis, Fabry's disease, Gaucher's disease, Tay-Sachs disease and Sjogren-Larsson's syndrome. The composition may take the form e.g. of creams, ointments, lotions, capsules, pearls, ovules, mascara, eyewashes, toothpaste, mouth washes, lipsticks, liposomes, soaps, shaving soaps, tonics, douches, enteroclysis solutions, shampoos, anti-dandruff preparations, impregnated and/or medicated bandages or gauzes, patches, medicated emulsions or transdermal gels, or patches (all

claimed).
Dwg.0/1
FILE SEGMENT: CPI
FIELD AVAILABILITY: AB
MANUAL CODES: CPI: B04-L05A; B14-N17C; B14-R01; D05-A02; D08-A05; D08-B01; D08-B04; D08-B08; D08-B09A; D09-C04B; D11-C

L161 ANSWER 45 OF 127 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1998-292083 [26] WPIX
DOC. NO. CPI: C1998-090789
TITLE: Novel compounds B-5354a, B-5354b and B-5354c used as e.g. immunosuppressants - are produced by culturing bacterium SANK 71896 and recovering the product from the medium.
DERWENT CLASS: B05 D16
PATENT ASSIGNEE(S): (SANY) SANKYO CO LTD
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
JP 10101630	A	19980421	(199826)*		7	C07C229-64<--

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE	
JP 10101630	A	JP 1996-259446	19960930	<--

PRIORITY APPLN. INFO: **JP 1996-259446**
19960930
INT. PATENT CLASSIF.:
MAIN: C07C229-64
SECONDARY: A61K031-245
ADDITIONAL: **C12N009-99**
BASIC ABSTRACT:
JP 10101630 A UPAB: 19980701
Novel compounds B-5354a of formula (I), B-5354b of formula (II) and B-5354c of formula (III), and their salts are new. Also claimed is the strain SANK 71896 (FERM BP-5356) able to produce (I), (II) and/or (III).
(I), (II) and/or (III) are prepared by culturing a bacterium having ability to produce (I), (II) and/or (III), and collecting the product from the cultured (claimed).
USE - (I)-(III) are useful as medicines, especially **sphingosine**-kinase **inhibitors**. They are useful for **prevention** or treatment of **arteriosclerosis**, diabetes, thrombosis, inflammation, cancer, cancer metastasis, **restenosis** after PTCA, and as immunosuppressants.
Dwg.0/0
FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B10-B02A; B14-C03; B14-D06; **B14-F04**; **B14-F07**; B14-G02; B14-H01; B14-S04; D05-C; D05-H04

L161 ANSWER 46 OF 127 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1997-399467 [37] WPIX
DOC. NO. CPI: C1997-128483
TITLE: New **sphingosine** kinase **inhibitor** F-12509A - for **prevention** and treatment of

arteriosclerosis, diabetes, thrombosis etc..
DERWENT CLASS: B05 D16
PATENT ASSIGNEE(S): (SANY) SANKYO CO LTD
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
JP 09176083	A	19970708	(199737)*		9	C07C050-28<--

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE	
JP 09176083	A	JP 1995-342524	19951228	<--

PRIORITY APPLN. INFO: **JP 1995-342524**
19951228
INT. PATENT CLASSIF.:
MAIN: C07C050-28
SECONDARY: A61K031-12; **C12N009-99**; C12P007-66
INDEX: C12P007-66, C12R001:6
BASIC ABSTRACT:
JP 09176083 A UPAB: 19971113
Sphingosin kinase **inhibiting** compound F-12509A of formula (I) and its salts are new:
USE - F-12509A has an **inhibitory** action to **sphingosine** kinase and medicines containing F-12509A are useful for **prevention** or treatment of **arteriosclerosis**, diabetes, thrombosis, inflammatory diseases, autoimmune diseases, progress or metastasis of cancer and **restenosis** after PTCA.
Dwg.0/0
FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B10-A06; B14-C03; B14-D06; **B14-F01E**; **B14-F04**; **B14-F07**; B14-G02D; B14-H01; B14-S04; D05-C

L161 ANSWER 47 OF 127 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1996-175685 [18] WPIX
DOC. NO. CPI: C1996-055459
TITLE: New cpd. F-11263 **inhibiting** **sphingomyelinase** - useful for treating osteoporosis, thrombosis, inflammation, nephritis, cachexia, HIV and Alzheimer's disease, etc..
DERWENT CLASS: B05 D16
PATENT ASSIGNEE(S): (SANY) SANKYO CO LTD
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
JP 08053387	A	19960227	(199618)*		7	C07C050-28<--

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE	
JP 08053387	A	JP 1994-189722	19940812	<--

PRIORITY APPLN. INFO: **JP 1994-189722**
19940812
INT. PATENT CLASSIF.:
MAIN: C07C050-28
SECONDARY: C12N001-20; C12P007-66
ADDITIONAL: A61K031-12; A61K035-74; **C12N009-99**
INDEX: C12N001-20, C12R001:645; C12P007-66, C12R001:6
BASIC ABSTRACT:
JP 08053387 A UPAB: 19960503
Cpd. F-11263 (2(3-hydroxy-3-methyl-2-butenyl)-quinone) of formula (I) is new.
(I) can be prepared by incubating an F-11263 producing strain of Acremonium (especially: Acremonium sp. SANK11894, FERM BP-4683) and recovering F-11263 from the culture broth.
USE - (I) may be used as a drug in the treatment of HIV, diabetes mellitus, **arteriosclerosis**, osteoporosis, thrombosis, inflammation, respiratory diseases, diseases of the thyroid gland, Alzheimer's disease, hepatitis, nephritis, leukaemia or cachexia, or as an immunosuppressive agent or diuretic. The dosage of (I) is 50-1000 mg/day. (I) may be administered orally or parenterally as tablets, capsules, granules, syrup, injection, eye-lotion, or suppositories.
Dwg.0/0
FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B10-A06; B14-A02B1; B14-C03; B14-D07A;
B14-F04; **B14-F07**; B14-G02;
B14-H01A; B14-J01A4; B14-K01; B14-N01; B14-N10;
B14-N11; B14-N12; B14-S04; D05-C

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YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, PASCAL, LIFESCI, BIOENG, BIOTECHDS, DRUGU, SCISEARCH' - CONTINUE? (Y)/N:y

L161 ANSWER 48 OF 127 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2000054403 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10585401
TITLE: **Sphingosine** 1-phosphate **stimulates** cell migration through a G(i)-coupled cell surface receptor. Potential involvement in angiogenesis.
AUTHOR: Wang F; Van Brocklyn J R; Hobson J P; Movafagh S; Zukowska-Grojec Z; Milstien S; Spiegel S
CORPORATE SOURCE: Department of Biochemistry, Georgetown University Medical Center, Washington, D.C. 20007, USA.
CONTRACT NUMBER: 1P30-CA-51008 (NCI)
CA61774 (NCI)
F32GM19209 (NIGMS)
SOURCE: The Journal of biological chemistry, **(1999 Dec 10)** Vol. 274, No. 50, pp. 35343-50.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 24 Jan 2000

Last Updated on STN: 19 Sep 2002
Entered Medline: 13 Jan 2000

ED Entered STN: 24 Jan 2000
Last Updated on STN: 19 Sep 2002
Entered Medline: 13 Jan 2000

AB **Sphingosine** 1-phosphate (SPP) has been shown to **inhibit** chemotaxis of a variety of cells, in some cases through intracellular actions, while in others through receptor-mediated effects. Surprisingly, we found that low concentrations of SPP (10-100 nM) increased chemotaxis of HEK293 cells overexpressing the G protein-coupled SPP receptor EDG-1. In agreement with previous findings in human breast cancer cells (Wang, F., Nohara, K., Olivera, O., Thompson, E. W., and Spiegel, S. (1999) Exp. Cell Res. 247, 17-28), SPP, at micromolar concentrations, inhibited chemotaxis of both vector- and EDG-1-overexpressing HEK293 cells. Nanomolar concentrations of SPP also induced a marked increase in chemotaxis of human umbilical vein endothelial cells (HUVEC) and bovine aortic endothelial cells (BAEC), which express the SPP receptors EDG-1 and EDG-3, while higher concentrations of SPP were less effective. **Treatment** with pertussis toxin, which ADP-ribosylates and inactivates G(i)-coupled receptors, blocked SPP-induced chemotaxis. Checkerboard analysis indicated that SPP stimulates both chemotaxis and chemokinesis. Taken together, these data suggest that SPP stimulates cell migration by binding to EDG-1. Similar to SPP, sphinganine 1-phosphate (dihydro-SPP), which also binds to this family of SPP receptors, enhanced chemotaxis; whereas, another structurally related lysophospholipid, lysophosphatidic acid, did not compete with SPP for binding nor did it have significant effects on chemotaxis of endothelial cells. Furthermore, SPP increased proliferation of HUVEC and BAEC in a pertussis toxin-sensitive manner. SPP and dihydro-SPP also stimulated tube formation of BAEC grown on collagen gels (in vitro angiogenesis), and potentiated tube formation induced by basic fibroblast growth factor. Pertussis toxin **treatment** blocked SPP-, but not bFGF-stimulated in vitro **angiogenesis.** Our results suggest that SPP may play a role in angiogenesis through binding to endothelial cell G(i)-coupled SPP receptors.

CT Animals
Aorta
Cattle
Cell Division: DE, drug effects
Cell Line
Cells, Cultured
Chemotaxis: DE, drug effects
*Chemotaxis: PH, physiology
DNA: BI, biosynthesis
DNA-Binding Proteins: GE, genetics
*DNA-Binding Proteins: PH, physiology
Dose-Response Relationship, Drug
Endothelium, Vascular: CY, cytology
Endothelium, Vascular: DE, drug effects
*Endothelium, Vascular: PH, physiology
Fibroblast Growth Factor 2: PD, pharmacology
*GTP-Binding Protein alpha Subunits, Gi-Go: PH, physiology
Humans
*I-kappa B Proteins
Immediate-Early Proteins: GE, genetics
*Immediate-Early Proteins: PH, physiology
Kinetics
*Lysophospholipids
Neovascularization, Physiologic: DE, drug effects
*Neovascularization, Physiologic: PH, physiology

*Receptors, Cell Surface: PH, physiology
*Receptors, G-Protein-Coupled
Receptors, Lysophospholipid
Recombinant Proteins: ME, metabolism
Research Support, U.S. Gov't, Non-P.H.S.
Research Support, U.S. Gov't, P.H.S.
Reverse Transcriptase Polymerase Chain Reaction
***Sphingosine: AA, analogs & derivatives**
Sphingosine: PK, pharmacokinetics
Sphingosine: PD, pharmacology
Transfection
Umbilical Veins

RN 103107-01-3 (Fibroblast Growth Factor 2); **123-78-4 (Sphingosine)** ; 139874-52-5 (NF-kappaB inhibitor alpha); **26993-30-6 (sphingosine 1-phosphate)**; 9007-49-2 (DNA)

CN 0 (DNA-Binding Proteins); 0 (I-kappa B Proteins); 0 (Immediate-Early Proteins); 0 (Lysophospholipids); 0 (Receptors, Cell Surface); 0 (Receptors, G-Protein-Coupled); 0 (Receptors, Lysophospholipid); 0 (Recombinant Proteins); EC 3.6.1.46 (GTP-Binding Protein alpha Subunits, Gi-Go)

L161 ANSWER 49 OF 127 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 1999242383 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10224298
TITLE: FK506 **prevents stroke-induced** generation of **ceramide** and apoptosis signaling.
AUTHOR: Herr I; Martin-Villalba A; Kurz E; Roncaioli P; Schenkel J; Cifone M G; Debatin K M
CORPORATE SOURCE: Division of Molecular Oncology, German Cancer Research Center, Heidelberg, Germany.. i.herr@dkfz-heidelberg.de
SOURCE: Brain research, **(1999 May 1)** Vol. 826, No. 2, pp. 210-9.
Journal code: 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 18 Jun 1999
Last Updated on STN: 3 Mar 2000
Entered Medline: 8 Jun 1999

ED Entered STN: 18 Jun 1999
Last Updated on STN: 3 Mar 2000
Entered Medline: 8 Jun 1999

AB **Ceramide** is a key **mediator** of apoptosis during the cellular stress response which is also involved in stroke-induced death. Transient occlusion of the middle cerebral artery (MCA) in rats led to a strong generation of ceramide as measured in thalamus and entorhinal cortex of the ischemic brain tissue. **Enhanced** levels of **ceramide** may be involved in apoptosis signaling following stroke since exogenously added synthetic C2-**ceramide** increased expression of c-jun and the death-**inducing** ligands (DILs) CD95-L, TRAIL and TNF-alpha in neuroblastoma cells. DILs in turn mediated death via binding to their respective receptors as concluded from diminished apoptosis upon blocking of the common pathway by dominant negative FADD. C2-**ceramide induced** both necrosis and apoptosis in a concentration-dependent manner corresponding to the situation present in the ischemic brain. The immunosuppressant FK506 **inhibited** the release of **ceramide**, expression of CD95-L and apoptosis in an in vitro and in vivo model for ischemia/reperfusion.

These data suggest that **ceramide** is a crucial initiator of death, e.g., by **induction** of DILs following stroke.

CT Check Tags: Male
Animals
*Apoptosis: DE, drug effects
Apoptosis Regulatory Proteins
Brain Chemistry: DE, drug effects
Brain Chemistry: GE, genetics
***Cerebrovascular Disorders: DT, drug therapy**
Cerebrovascular Disorders: ME, metabolism
*Enzyme Inhibitors: ME, metabolism
Enzyme Inhibitors: PD, pharmacology
Gene Expression: DE, drug effects
Humans
*Immunosuppressive Agents: PD, pharmacology
Ischemic Attack, Transient: DT, drug therapy
Ischemic Attack, Transient: ME, metabolism
Membrane Glycoproteins: GE, genetics
Necrosis
Neuroblastoma
Neurons: DE, drug effects
Neurons: PA, pathology
Neurons: PH, physiology
Proto-Oncogene Proteins c-jun: GE, genetics
Rats
Rats, Sprague-Dawley
Reperfusion Injury: DT, drug therapy
Reperfusion Injury: ME, metabolism
Signal Transduction: DE, drug effects
***Sphingosine: AA, analogs & derivatives**
Sphingosine: BI, biosynthesis
Sphingosine: PD, pharmacology
*Tacrolimus: PD, pharmacology
Tumor Cells, Cultured: DE, drug effects
Tumor Cells, Cultured: ME, metabolism
Tumor Necrosis Factor-alpha: GE, genetics
Up-Regulation: DE, drug effects
RN 109581-93-3 (Tacrolimus); **123-78-4 (Sphingosine)**
CN 0 (Apoptosis Regulatory Proteins); 0 (Enzyme Inhibitors); 0 (Fas ligand); 0 (Immunosuppressive Agents); 0 (Membrane Glycoproteins); 0 (N-acetylsphingosine); 0 (Proto-Oncogene Proteins c-jun); 0 (TNF-related apoptosis-inducing ligand); 0 (Tumor Necrosis Factor-alpha)

L161 ANSWER 50 OF 127 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 96185799 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8604008
TITLE: Myocardial protection by N,N,N-**trimethylsphingosine** in ischemia reperfusion injury is **mediated** by **inhibition** of P-selectin.
AUTHOR: Scalia R; Murohara T; Delyani J A; Nossuli T O; Lefer A M
CORPORATE SOURCE: Department of Physiology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA, USA.
CONTRACT NUMBER: GM45435 (NIGMS)
SOURCE: Journal of leukocyte biology, **(1996 Mar)** Vol. 59, No. 3, pp. 317-24.
Journal code: 8405628. ISSN: 0741-5400.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199605
ENTRY DATE: Entered STN: 24 May 1996
Last Updated on STN: 3 Feb 1997
Entered Medline: 15 May 1996

ED Entered STN: 24 May 1996
Last Updated on STN: 3 Feb 1997
Entered Medline: 15 May 1996

AB Polymorphonuclear leukocytes (PMNs) play an important role in myocardial ischemia/reperfusion (MI/R) injury. We examined the cardioprotective **effects** of N,N,N-**trimethylsphingosine** (TMS) in a murine model of MI (20 min) and R (24 h) injury in vivo, focusing on leukocyte-endothelial interactions. TMS is a synthetic N-methylated **sphingosine** derivative that has protein kinase C **inhibitory** activity and has been shown to prevent leukocyte activation. TMS (18 microgram/kg), **administered** intravenously 1 min prior to **reperfusion**, significantly attenuated **myocardial** necrotic injury assessed by myocardial creatine kinase loss compared with MI/R rats receiving only vehicle ($P<0.001$). Cardiac myeloperoxidase activity, an index of PMN accumulation in the ischemic myocardium, was also significantly attenuated by TMS compared with rats receiving vehicle ($P<0.001$). We further examined whether TMS can attenuate leukocyte-endothelial interaction by intravital microscopy. TMS significantly attenuated NG-nitro-L-arginine-methyl ester (L-NAME)-stimulated PMN rolling and adherence to the rat microvascular endothelium. This action of TMS appears to be mediated by reduction of P-selectin expression because immunohistochemical analysis demonstrated that TMS significantly attenuated endothelial P-selectin expression in the L-NAME-superfused rat mesenteric microvasculature. Similarly, TMS markedly attenuated rapid P-selectin expression in rat platelets stimulated with either thrombin or L-NAME assessed by flow cytometry. In conclusion, TMS seems to be an effective **cardioprotective** agent by inhibiting early leukocyte-endothelial interaction, thus **preventing** leukocyte accumulation in the **ischemic reperfused myocardium.**

CT Check Tags: Male
Animals
Blood Platelets: ME, metabolism
Creatine Kinase: ME, metabolism
Endothelium, Vascular: CY, cytology
Microcirculation: CY, cytology
***Myocardial Infarction: DT, drug therapy**
Myocardium: EN, enzymology
Neutrophils: EN, enzymology
*P-Selectin: ME, metabolism
Peroxidase: ME, metabolism
*Platelet Aggregation Inhibitors: PD, pharmacology
Rats
Rats, Sprague-Dawley
*Reperfusion Injury: PC, prevention & control
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
***Sphingosine: AA, analogs & derivatives**
Sphingosine: PD, pharmacology
Sphingosine: TU, therapeutic use

RN **123-78-4 (Sphingosine)**; 138686-73-4 (N,N,N-trimethylsphingosine)

CN 0 (P-Selectin); 0 (Platelet Aggregation Inhibitors); EC 1.11.1.7 (Peroxidase); EC 2.7.3.2 (Creatine Kinase)

L161 ANSWER 51 OF 127 MEDLINE on STN

ACCESSION NUMBER: 2004523681 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15494205
TITLE: In vitro and in vivo **modulation** of vascular barrier integrity by **sphingosine** 1-phosphate: mechanistic insights.
AUTHOR: McVerry Bryan J; Garcia Joe G N
CORPORATE SOURCE: Center for Translational Respiratory Medicine, Johns Hopkins University School of Medicine, Division of Pulmonary and Critical Care Medicine, 1830 E. Monument Street Room 527, Baltimore, MD 21287, USA.
CONTRACT NUMBER: HL58064 (NHLBI)
SOURCE: Cellular signalling, (2005 Feb) Vol. 17, No. 2, pp. 131-9. Ref: 63
Journal code: 8904683. ISSN: 0898-6568.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200504
ENTRY DATE: Entered STN: 22 Oct 2004
Last Updated on STN: 27 Apr 2005
Entered Medline: 26 Apr 2005

ED Entered STN: 22 Oct 2004
Last Updated on STN: 27 Apr 2005
Entered Medline: 26 Apr 2005

AB **Sphingosine** 1-phosphate (S1P), a biologically active lipid growth factor, **induces** robust endothelial cell activation resulting in cellular locomotion, vascular maturation and angiogenesis. Recent work by our laboratory has demonstrated S1P to enhance the cellular barrier function of the vascular endothelium. S1P-induced modulation of vascular permeability is effected through profound cytoskeletal reorganization initiated by cell surface receptor-mediated G protein activation and downstream signaling via the Rho family of small GTPases. The details of the downstream signaling mechanism remain an active area of in vitro investigation. Translational investigation suggests a profound impact of S1P **administration** in the modulation of edema formation in disease state manifest as acute inflammatory lung injury in which increased vascular permeability is a hallmark feature. These data support an exciting potential **therapeutic** role for S1P in **vascular** barrier enhancement necessary for the **treatment** of critically ill patients.

CT Adherens Junctions: DE, drug effects
Adherens Junctions: ME, metabolism
Adherens Junctions: PH, physiology
Angiogenesis Inducing Agents: ME, metabolism
Angiogenesis Inducing Agents: PD, pharmacology
Animals
Anti-Inflammatory Agents: PD, pharmacology
Anti-Inflammatory Agents: TU, therapeutic use
Capillary Permeability: DE, drug effects
*Capillary Permeability: PH, physiology
Cytoskeleton: DE, drug effects
Cytoskeleton: ME, metabolism
Cytoskeleton: PH, physiology
Endothelium, Vascular: DE, drug effects
Endothelium, Vascular: ME, metabolism
Endothelium, Vascular: PH, physiology
Extracellular Matrix: DE, drug effects
Extracellular Matrix: ME, metabolism

Extracellular Matrix: PH, physiology
Focal Adhesions: DE, drug effects
Focal Adhesions: ME, metabolism
Focal Adhesions: PH, physiology
Humans
Lysophospholipids: PD, pharmacology
*Lysophospholipids: PH, physiology
Lysophospholipids: TU, therapeutic use
Models, Biological
Research Support, U.S. Gov't, P.H.S.
Respiratory Distress Syndrome, Adult: DT, drug therapy
Respiratory Distress Syndrome, Adult: PP, physiopathology
Signal Transduction: PH, physiology
***Sphingosine: AA, analogs & derivatives**
Sphingosine: PD, pharmacology
***Sphingosine: PH, physiology**
Sphingosine: TU, therapeutic use
rac GTP-Binding Proteins: PH, physiology
RN **123-78-4 (Sphingosine); 26993-30-6 (sphingosine 1-phosphate)**
CN 0 (Angiogenesis Inducing Agents); 0 (Anti-Inflammatory Agents); 0 (Lysophospholipids); EC 3.6.5.2 (rac GTP-Binding Proteins)

L161 ANSWER 52 OF 127 MEDLINE on STN
ACCESSION NUMBER: 2001103442 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10952678
TITLE: **Sphingosine**-1-phosphate **reduces** rat renal and mesenteric blood flow in vivo in a pertussis toxin-sensitive manner.
AUTHOR: Bischoff A; Czyborra P; Meyer Zu Heringdorf D; Jakobs K H; Michel M C
CORPORATE SOURCE: Department of Medicine, Universitatsklinikum Essen, 45122 Essen, Germany. Institute of Pharmacology, Universitatsklinikum Essen, 45122 Essen, Germany.
SOURCE: British journal of pharmacology, **(2000 Aug)** Vol. 130, No. 8, pp. 1878-83.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 18 Dec 2002
Entered Medline: 8 Feb 2001
ED Entered STN: 22 Mar 2001
Last Updated on STN: 18 Dec 2002
Entered Medline: 8 Feb 2001
AB **Sphingolipids** such as **sphingosine**-1-phosphate (SPP) and **sphingosylphosphorylcholine** constrict isolated rat intrarenal and mesenteric microvessels in vitro. The present study investigates their effects on the cardiovascular system in vivo in anaesthetized rats. The animals were given intravenous or intrarenal arterial bolus injections of **sphingolipids** (0.1-100 microg kg(-1)) with subsequent measurements of mean arterial pressure, heart rate and renal and mesenteric blood flows (RBF, MBF) using a pressure transducer and electromagnetic flow probes, respectively. Intravenous injection of SPP rapidly (within 30 s), transiently and dose-dependently reduced RBF (maximally -4.0+/-0.3 ml min(-1)) and MBF (maximally -1.4+/-0.2 ml min(-1)), without affecting mean arterial pressure or heart

rate. Other **sphingolipids** had no significant **effect.** Intrarenal **arterial** SPP **administration** caused greater blood flow reductions (maximally -6.4+/-0.3 ml min(-1)) than systemic **administration.** Upon intrarenal **administration,** **sphingosylphos**- phorylcholine also lowered RBF (maximally -2.8+/-0.6 ml min(-1)), while the other **sphingolipids** remained without **effect.** Pretreatment with pertussis toxin (PTX, 10 microg kg(-1)) 3 days before the acute experiment abolished the SPP-induced reductions of RBF and MBF. These data demonstrate, that SPP is a potent vasoconstrictor in vivo, particularly in the renal vasculature, while the other structurally related **sphingolipids** had little if any **effects.** The PTX-sensitivity strongly suggests that the effects of SPP on renal and mesenteric blood flow are mediated by receptors coupled to G(i)-type G-proteins.

CT Check Tags: Male
Animals
Blood Pressure: DE, drug effects
Dose-Response Relationship, Drug
Heart Rate: DE, drug effects
Kidney: BS, blood supply
*Lysophospholipids
Mesentery: BS, blood supply
*Pertussis Toxin
*Phosphorylcholine: AA, analogs & derivatives
Phosphorylcholine: PD, pharmacology
***Psychosine: AA, analogs & derivatives**
Psychosine: PD, pharmacology
Rats
Rats, Wistar
*Renal Circulation: DE, drug effects
Research Support, Non-U.S. Gov't
***Sphingosine: AA, analogs & derivatives**
***Sphingosine: PD, pharmacology**
*Splanchnic Circulation: DE, drug effects
*Virulence Factors, Bordetella: PD, pharmacology

RN 10216-23-6 (sphingosine phosphorylcholine); 107-73-3 (Phosphorylcholine); **123-78-4 (Sphingosine)**; 2238-90-6 (Psychosine); **26993-30-6 (sphingosine 1-phosphate)**; 52050-17-6 (sphingosyl beta-glucoside)

CN 0 (Lysophospholipids); 0 (Virulence Factors, Bordetella); EC 2.4.2.31 (Pertussis Toxin)

L161 ANSWER 53 OF 127 MEDLINE on STN
ACCESSION NUMBER: 2001016699 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10875754
TITLE: **Effects** of **sphingosine** 1-phosphate, a naturally occurring biologically active lysophospholipid, on the rat cardiovascular system.
AUTHOR: Sugiyama A; Aye N N; Yatomi Y; Ozaki Y; Hashimoto K
CORPORATE SOURCE: Department of Pharmacology, Yamanashi Medical University Nakakoma-gun, Japan.
SOURCE: Japanese journal of pharmacology, **(2000 Apr)** Vol. 82, No. 4, pp. 338-42.
Journal code: 2983305R. ISSN: 0021-5198.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001

Entered Medline: 7 Nov 2000

ED Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 7 Nov 2000

AB Recent studies have indicated that **sphingosine** 1-phosphate (Sph-1-P) is released into the blood flow from activated platelets upon stimulation to exhibit a wide spectrum of biological functions. The purpose of the present study was to assess the acute cardiovascular effects of circulating Sph-1-P in the in vivo rat model. Intravenous **administration** of Sph-1-P decreased the **heart** rate, ventricular contraction and blood pressure, while it hardly affected the atrioventricular and intraventricular conduction. Sph-1-P did not affect the adenylate cyclase activities of the membrane preparations made from the right atrium and left ventricle. These results suggest that functional receptors like lysophospholipid receptor Edg-1, which can inhibit adenylate cyclase via Gi protein, are lacking in the rat heart. Moreover, these observations will provide a clue to better understand the various types of Sph-1-P-related pathophysiological processes.

CT Check Tags: Male
Adenylate Cyclase: ME, metabolism
Animals
Blood Pressure: DE, drug effects
***Cardiovascular System: DE, drug effects**
Electrocardiography: DE, drug effects
Heart Rate: DE, drug effects
*Lysophospholipids
Myocardium: EN, enzymology
Rats
Rats, Sprague-Dawley
Research Support, Non-U.S. Gov't
Signal Transduction: DE, drug effects
Signal Transduction: PH, physiology
***Sphingosine: AA, analogs & derivatives**
***Sphingosine: PD, pharmacology**
Ventricular Function, Left: DE, drug effects
Ventricular Pressure: DE, drug effects

RN **123-78-4 (Sphingosine); 26993-30-6 (sphingosine 1-phosphate)**

CN 0 (Lysophospholipids); EC 4.6.1.1 (Adenylate Cyclase)

L161 ANSWER 54 OF 127 MEDLINE on STN

ACCESSION NUMBER: 2000426429 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10948061
TITLE: Ceramide-coated balloon catheters limit neointimal hyperplasia after stretch injury in carotid arteries.
AUTHOR: Charles R; Sandirasegarane L; Yun J; Bourbon N; Wilson R; Rothstein R P; Levison S W; Kester M
CORPORATE SOURCE: Department of Pharmacology, Pennsylvania State University, Milton S. Hershey Medical Center, Hershey, PA, USA.
CONTRACT NUMBER: RO1 DK53715 (NIDDK)
SOURCE: Circulation research, **(2000 Aug 18)** Vol. 87, No. 4, pp. 282-8.
Journal code: 0047103. ISSN: 0009-7330.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 22 Sep 2000
Last Updated on STN: 10 Dec 2002

Entered Medline: 12 Sep 2000
ED Entered STN: 22 Sep 2000
Last Updated on STN: 10 Dec 2002
Entered Medline: 12 Sep 2000
AB Neointimal hyperplasia at the site of surgical intervention is a common and deleterious complication of surgery for cardiovascular diseases. We hypothesized that direct delivery of a cell-permeable growth-arresting lipid via the balloon tip of an embolectomy catheter would limit neointimal hyperplasia after stretch injury. We have previously demonstrated that **sphingolipid**-derived **ceramide** arrested the growth of smooth muscle cell pericytes in vitro. Here, we show that **ceramide**-coated balloon catheters significantly **reduced** neointimal hyperplasia **induced** by balloon angioplasty in rabbit carotid arteries in vivo. This **ceramide treatment** decreased the number of **vascular** smooth muscle cells entering the cell cycle without inducing apoptosis. In situ autoradiographic studies demonstrated that inflating the balloon catheter forced cell-permeable **ceramide** into the intimal and medial layers of the artery. Intercalation of **ceramide** into vascular smooth muscle cells correlated with rapid **inhibition** of trauma-associated phosphorylation of extracellular signal-regulated kinase and protein kinase B. These studies demonstrate the utility of cell-permeable **ceramide** as a novel **therapy** for **reducing** neointimal hyperplasia after balloon angioplasty.
CT *Angioplasty, Transluminal, Percutaneous Coronary: AE, adverse effects
Angioplasty, Transluminal, Percutaneous Coronary: MT, methods
Animals
Apoptosis: PH, physiology
***Carotid Artery Injuries: DT, drug therapy**
Carotid Artery Injuries: ME, metabolism
*Carotid Artery Injuries: PA, pathology
Carotid Stenosis: DT, drug therapy
Carotid Stenosis: ME, metabolism
Carotid Stenosis: PA, pathology
***Ceramides: PD, pharmacology**
Disease Models, Animal
Hyperplasia
Mitogen-Activated Protein Kinases: ME, metabolism
Muscle, Smooth, Vascular: EN, enzymology
Muscle, Smooth, Vascular: IN, injuries
Muscle, Smooth, Vascular: PA, pathology
Postoperative Complications: DT, drug therapy
Postoperative Complications: PA, pathology
Postoperative Complications: PC, prevention & control
Rabbits
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
Tunica Intima: EN, enzymology
Tunica Intima: IN, injuries
Tunica Intima: PA, pathology
CN 0 (Ceramides); 0 (N-caproylsphingosine); 0 (dihydroceramide); EC 2.7.1.37 (Mitogen-Activated Protein Kinases)

L161 ANSWER 55 OF 127 MEDLINE on STN
ACCESSION NUMBER: 2000445976 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10997751
TITLE: Involvement of caspase 3- and 8-like proteases in **ceramide-induced** apoptosis of cardiomyocytes.
AUTHOR: Wang J; Zhen L; Klug M G; Wood D; Wu X; Mizrahi J

CORPORATE SOURCE: Cardiovascular Division, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285, USA.
SOURCE: Journal of cardiac failure, **(2000 Sep)** Vol. 6, No. 3, pp. 243-9.
Journal code: 9442138. ISSN: 1071-9164.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 9 Jan 2001
ED Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 9 Jan 2001

AB **Ceramides** are the metabolic products of **sphingolipids** of the eukaryotic cell membranes and are believed to function as signaling molecules in a variety of biological processes. **Ceramide induces** apoptosis in cultured cardiomyocytes. However, the molecular pathway underlying **ceramide-induced** apoptosis is not clear. In this study, we investigated the role of the cysteinyl aspartate-specific proteases (caspases) in cardiomyocyte apoptosis **induced** by **ceramide. Treatment** of in vitro cultured rat neonatal **cardiomyocytes** with **ceramide** results in robust cell death, of which the majority is apoptotic, as shown by positive staining for terminal deoxyribonuclease transferase-mediated deoxyuridine triphosphate nick end-labeling and the appearance of pyknotic nuclei with Hoechst staining. Caspase 3- and 8-like protease activities are **induced** in **cardiomyocytes** by **ceramide treatment.** Addition of the tetrapeptide **inhibitors** for caspases attenuated **ceramide-induced** apoptosis. The nonselective caspase inhibitor (B-D-FMK) and the caspase 3 (Z-DEVD-FMK) and caspase 8 (Z-IETD-FMK) **inhibitors reduced ceramide-induced** cardiomyocyte death and significantly **inhibited** the activation of caspase 3. However, the inhibitors specific for caspases 1, 2, 4, 6, and 9 have no significant effects on cardiomyocyte survival under the same conditions. These data suggest that caspases 3- and 8-related proteases are involved in **ceramide-induced** cardiomyocyte apoptosis.

CT Animals
*Apoptosis
Apoptosis: DE, drug effects
Caspases: AI, antagonists & inhibitors
*Caspases: ME, metabolism
***Ceramides: AE, adverse effects**
Cysteine Proteinase Inhibitors: PD, pharmacology
Cytoprotection
Heart: DE, drug effects
In Vitro
*Myocardium: ME, metabolism
*Myocardium: PA, pathology
Oligopeptides: PD, pharmacology
Rats
Rats, Sprague-Dawley
CN 0 (Ceramides); 0 (Cysteine Proteinase Inhibitors); 0 (Oligopeptides); 0 (benzoylcarbonyl-aspartyl-glutamyl-valyl-aspartyl-fluoromethyl ketone); 0 (benzyloxycarbonyl-isoleucyl-glutamyl-threonyl-aspartic acid fluoromethyl ketone); EC 3.4.22.- (Caspases); EC 3.4.22.- (caspase 8); EC 3.4.22.-

(caspase 9); EC 3.4.22.- (caspase-3)

L161 ANSWER 56 OF 127 MEDLINE on STN
ACCESSION NUMBER: 2001416470 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11465070
TITLE: **Modulation** of the **ceramide** level, a novel **therapeutic** concept?.
AUTHOR: Claus R; Russwurm S; Meisner M; Kinscherf R; Deigner H P
CORPORATE SOURCE: Institute of Pharmaceutical Chemistry, University of Heidelberg, Germany.
SOURCE: Current drug targets, **(2000 Sep)** Vol. 1, No. 2, pp. 185-205. Ref: 225
Journal code: 100960531. ISSN: 1389-4501.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 3 Sep 2001
Last Updated on STN: 3 Sep 2001
Entered Medline: 30 Aug 2001

ED Entered STN: 3 Sep 2001
Last Updated on STN: 3 Sep 2001
Entered Medline: 30 Aug 2001

AB The **sphingomyelin** (SM) pathway is an ubiquitous and evolutionarily conserved signaling system in which **ceramide** (CA), generated from SM by the action of various isoforms of **sphingomyelinases** (**SMases**) functions as an important second messenger. Recent evidence suggests that branching pathways of **sphingolipid** metabolism **mediate** either apoptotic or mitogenic responses depending on cell type and the nature of the stimulus. Events involving SM metabolites and CA in particular include proliferation, differentiation and growth arrest as well as the induction of apoptosis. An improved understanding of **SMase**-dependent signaling may afford relevant insights into the pathogenesis of diseases and provide novel strategies and selective targets for a **therapeutic** intervention e.g. in cancer, **cardiovascular** and neurodegenerative diseases, HIV and septic shock. This article briefly summarizes the role of **SMases** in signaling pathways, its potential contribution in the development and maintenance of various pathobiological states and analyzes the perspective of a potentially isotype-specifc **inhibition** of **SMases** as a novel **therapeutic** concept.

CT Animals
Antineoplastic Agents: PD, pharmacology
Arteriosclerosis: DT, drug therapy
Arteriosclerosis: ET, etiology
Arteriosclerosis: ME, metabolism
Cell Death: DE, drug effects
Cell Death: PH, physiology
Ceramides: ME, metabolism
***Ceramides: PH, physiology**
Enzyme Inhibitors: PD, pharmacology
Enzyme Inhibitors: TU, therapeutic use
HIV Infections: DT, drug therapy
HIV Infections: ET, etiology
HIV Infections: ME, metabolism
Humans
Neurodegenerative Diseases: DT, drug therapy

Neurodegenerative Diseases: ET, etiology
Neurodegenerative Diseases: ME, metabolism
Research Support, Non-U.S. Gov't
Sepsis: DT, drug therapy
Sepsis: ET, etiology
Sepsis: ME, metabolism
Signal Transduction: DE, drug effects
*Signal Transduction: PH, physiology
Sphingomyelin Phosphodiesterase: DE, drug effects
Sphingomyelin Phosphodiesterase: ME, metabolism
***Sphingomyelin Phosphodiesterase: PH, physiology**
Sphingomyelins: ME, metabolism
***Sphingomyelins: PH, physiology**
Tumor Cells, Cultured: DE, drug effects
Tumor Cells, Cultured: ME, metabolism
Tumor Necrosis Factor-alpha: DE, drug effects
Tumor Necrosis Factor-alpha: ME, metabolism
CN 0 (Antineoplastic Agents); 0 (Ceramides); 0 (Enzyme Inhibitors); 0 (Sphingomyelins); 0 (Tumor Necrosis Factor-alpha); EC 3.1.4.12 (Sphingomyelin Phosphodiesterase)

L161 ANSWER 57 OF 127 MEDLINE on STN
ACCESSION NUMBER: 1999393475 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10463940
TITLE: L-carnitine **prevents** doxorubicin-**induced** apoptosis of **cardiac** myocytes: role of **inhibition** of **ceramide** generation.
AUTHOR: Andrieu-Abadie N; Jaffrezou J P; Hatem S; Laurent G; Levade T; Mercadier J J
CORPORATE SOURCE: INSERM Unit 460, UFR de Medecine X. Bichat, Paris, France.. andrieu@bichat.inserm.fr
SOURCE: The FASEB journal : official publication of the Federation of American Societies for Experimental Biology, **(1999 Sep)** Vol. 13, No. 12, pp. 1501-10.
Journal code: 8804484. ISSN: 0892-6638.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 5 Oct 1999
Last Updated on STN: 5 Oct 1999
Entered Medline: 17 Sep 1999
ED Entered STN: 5 Oct 1999
Last Updated on STN: 5 Oct 1999
Entered Medline: 17 Sep 1999
AB Besides the well-documented effect of the **chemotherapeutic** drug doxorubicin on free radical generation, the exact signaling mechanisms by which it causes cardiac damage remain largely unknown and are of fundamental importance in understanding anthracycline cardiotoxicity. In this study, we describe that a 1 h **treatment** of isolated adult rat **cardiac** myocytes with doxorubicin (0.5 microM) induced DNA fragmentation associated with the classical morphological features of apoptosis observed after 7 days of culture. The doxorubicin toxicity was preceded by an increase in intracellular **ceramide** levels with a concurrent decrease in **sphingomyelin.** Anthracycline-**induced ceramide** accumulation resulted from the activation of a **sphingomyelinase** assayed under acidic conditions, an **effect** related to an increase in V(max). Pretreatment of cardiac myocytes with L-carnitine (200 microgram/ml), a

compound known for its protective effect on cardiac metabolic injuries, was found to dose-dependently **inhibit** the doxorubicin-**induced sphingomyelin** hydrolysis and **ceramide** generation as well as subsequent cell death. However, L-carnitine did not protect cardiac myocytes from apoptosis **induced** by exogenous cell-permeant **ceramide.** L-carnitine pretreatment did not affect the **sphingomyelinase** basal activity but abolished the doxorubicin-**induced** increase in V(max). Moreover, in vitro studies conducted on cell extracts or with purified acid **sphingomyelinase** demonstrated that L-carnitine exerted a dose-dependent, **sphingomyelinase inhibitory effect** (through V(max) **reduction**). Taken together, these findings show that by **inhibiting** a (perhaps novel) drug-activated acid **sphingomyelinase** and **ceramide** generation, L-carnitine can **prevent** doxorubicin-**induced** apoptosis of **cardiac** myocytes.

CT Check Tags: Male
Animals
*Apoptosis: DE, drug effects
*Carnitine: PD, pharmacology
Cells, Cultured
***Ceramides: ME, metabolism**
DNA Fragmentation: DE, drug effects
*Doxorubicin: TO, toxicity
***Heart: DE, drug effects**
Kinetics
*Myocardium: CY, cytology
*Myocardium: ME, metabolism
Rats
Rats, Wistar
Research Support, Non-U.S. Gov't
Sphingomyelin Phosphodiesterase: AI, antagonists & inhibitors
***Sphingomyelin Phosphodiesterase: ME, metabolism**

RN 23214-92-8 (Doxorubicin); 541-15-1 (Carnitine)
CN 0 (Ceramides); EC 3.1.4.12 (Sphingomyelin Phosphodiesterase)

L161 ANSWER 58 OF 127 MEDLINE on STN
ACCESSION NUMBER: 1998298174 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9632721
TITLE: Involvement of **de** novo **ceramide** biosynthesis in tumor necrosis factor-alpha/cycloheximide-**induced cerebral** endothelial cell death.
AUTHOR: Xu J; Yeh C H; Chen S; He L; Sensi S L; Canzoniero L M; Choi D W; Hsu C Y
CORPORATE SOURCE: Center for the Study of Nervous System Injury and Department of Neurology, Washington University School of Medicine, St. Louis, Missouri 63110, USA.
CONTRACT NUMBER: NS 28995 (NINDS)
NS 32636 (NINDS)
NS 37230 (NINDS)
SOURCE: The Journal of biological chemistry, **(1998 Jun 26)** Vol. 273, No. 26, pp. 16521-6.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 17 Aug 1998
Last Updated on STN: 17 Aug 1998

Entered Medline: 3 Aug 1998
ED Entered STN: 17 Aug 1998
Last Updated on STN: 17 Aug 1998
Entered Medline: 3 Aug 1998
AB Cytokines, including tumor necrosis factor-alpha (TNF-alpha), may **elicit** cytotoxic response through the **sphingomyelin-ceramide** signal transduction pathway by activation of **sphingomyelinases** and the subsequent release of **ceramide** : the universal lipid second messenger. **Treatment** of bovine **cerebral** endothelial cells (BCECs) with TNF-alpha for 16 h followed by cycloheximide (CHX) for 6 h resulted in an increase in **ceramide** accumulation, DNA fragmentation, and cell death. Application of a cell permeable **ceramide** analogue C2 **ceramide**, but not the biologically inactive C2 **dihydroceramide**, also **induced** DNA laddering and BCEC death in a concentration- and time-dependent manner. TNF-alpha/CHX-**mediated ceramide** production apparently is not a result of **sphingomyelin** hydrolysis because **sphingomyelin** content does not decrease in this death paradigm. In addition, an acidic **sphingomyelinase inhibitor**, desipramine, had no **effect** on TNF-alpha/CHX-**induced** cell death. However, addition of fumonisin B1, a selective **ceramide** synthase **inhibitor**, attenuated TNF-alpha/CHX-**induced** intracellular **ceramide** elevation and BCEC death. Together, these findings suggest that **ceramide** plays at least a partial role in this paradigm of BCEC death. Our results show, for the first time, that **ceramide** derived from **de** novo synthesis is an alternative mechanism to **sphingomyelin** hydrolysis in the BCEC death process initiated by TNF-alpha/CHX.
CT Animals
Cattle
Cell Death: DE, drug effects
Cells, Cultured
***Ceramides: BI, biosynthesis**
*Cerebrovascular Circulation
*Cycloheximide: PD, pharmacology
***Endothelium, Vascular: DE, drug effects**
Oxidoreductases: AI, antagonists & inhibitors
*Protein Synthesis Inhibitors: PD, pharmacology
Research Support, U.S. Gov't, Non-P.H.S.
Research Support, U.S. Gov't, P.H.S.
*Tumor Necrosis Factor-alpha: PD, pharmacology
RN 66-81-9 (Cycloheximide)
CN 0 (Ceramides); 0 (Protein Synthesis Inhibitors); 0 (Tumor Necrosis Factor-alpha); EC 1. (Oxidoreductases); EC 1.3.1.- (dihydroceramide desaturase)

L161 ANSWER 59 OF 127 MEDLINE on STN
ACCESSION NUMBER: 1999045661 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9826677
TITLE: Tumor necrosis factor-alpha **induces** adhesion molecule expression through the **sphingosine** kinase pathway.
AUTHOR: Xia P; Gamble J R; Rye K A; Wang L; Hii C S; Cockerill P; Khew-Goodall Y; Bert A G; Barter P J; Vadas M A
CORPORATE SOURCE: Division of Human Immunology, The Hanson Centre for Cancer Research, Institute of Medical and Veterinary Science and University of Adelaide, Adelaide, SA 5000, Australia.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, **(1998 Nov 24)** Vol. 95,

No. 24, pp. 14196-201.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 15 Jan 1999
Last Updated on STN: 15 Jan 1999
Entered Medline: 28 Dec 1998
ED Entered STN: 15 Jan 1999
Last Updated on STN: 15 Jan 1999
Entered Medline: 28 Dec 1998

AB The signaling pathways that couple tumor necrosis factor-alpha (TNFalpha) receptors to functional, especially inflammatory, responses have remained elusive. We report here that TNFalpha induces endothelial cell activation, as measured by the expression of adhesion protein E-selectin and vascular adhesion molecule-1, through the **sphingosine** kinase (SKase) signaling pathway. **Treatment** of human umbilical **vein** endothelial cells with TNFalpha resulted in a rapid SKase activation and **sphingosine** 1-phosphate (S1P) generation. S1P, but not **ceramide** or **sphingosine**, was a potent dose-dependent **stimulator** of adhesion protein expression. S1P was able to mimic the effect of TNFalpha on endothelial cells leading to extracellular signal-**regulated** kinases and NF-kappaB activation, whereas **ceramide** or **sphingosine** was not. Furthermore, N, N-**dimethylsphingosine**, an **inhibitor** of SKase, profoundly **inhibited** TNFalpha-**induced** extracellular signal-**regulated** kinases and NF-kappaB activation and adhesion protein expression. Thus we demonstrate that the SKase pathway through the generation of S1P is critically involved in mediating TNFalpha-induced endothelial cell activation.

CT Ca(2+)-Calmodulin Dependent Protein Kinase: ME, metabolism
Cells, Cultured
*E-Selectin: GE, genetics
Endothelium, Vascular: CY, cytology
Endothelium, Vascular: DE, drug effects
*Endothelium, Vascular: PH, physiology
Enzyme Activation
Gene Expression Regulation: DE, drug effects
Humans
JNK Mitogen-Activated Protein Kinases
Kinetics
*Lysophospholipids
*Mitogen-Activated Protein Kinases
NF-kappa B: ME, metabolism
*Phosphotransferases (Alcohol Group Acceptor): ME, metabolism
Research Support, Non-U.S. Gov't
Signal Transduction
Sphingomyelins: ME, metabolism
Sphingosine: AA, analogs & derivatives
Sphingosine: ME, metabolism
Sphingosine: PD, pharmacology
*Tumor Necrosis Factor-alpha: PD, pharmacology
Umbilical Veins
*Vascular Cell Adhesion Molecule-1: GE, genetics
RN 122314-67-4 (N,N-dimethylsphingosine); **123-78-4 (Sphingosine)**; **26993-30-6 (sphingosine 1-phosphate)**
CN 0 (E-Selectin); 0 (Lysophospholipids); 0 (N-acetylsphingosine); 0 (NF-kappa B); 0 (Sphingomyelins); 0 (Tumor Necrosis Factor-alpha); 0

(Vascular Cell Adhesion Molecule-1); EC 2.7.1 (Phosphotransferases (Alcohol Group Acceptor)); EC 2.7.1.- (sphingosine kinase); EC 2.7.1.123 (Ca(2+)-Calmodulin Dependent Protein Kinase); EC 2.7.1.37 (JNK Mitogen-Activated Protein Kinases); EC 2.7.1.37 (Mitogen-Activated Protein Kinases)

L161 ANSWER 60 OF 127 MEDLINE on STN
ACCESSION NUMBER: 1998211999 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9545302
TITLE: Oxidized low density lipoprotein induces apoptosis in cultured human umbilical vein endothelial cells by common and unique mechanisms.
AUTHOR: Harada-Shiba M; Kinoshita M; Kamido H; Shimokado K
CORPORATE SOURCE: National Cardiovascular Center Research Institute, 7-1 Fujishirodai 5-chome, Suita, Osaka 565-8565, Japan.
SOURCE: The Journal of biological chemistry, **(1998 Apr 17)** Vol. 273, No. 16, pp. 9681-7.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 29 May 1998
Last Updated on STN: 3 Mar 2000
Entered Medline: 21 May 1998

ED Entered STN: 29 May 1998
Last Updated on STN: 3 Mar 2000
Entered Medline: 21 May 1998

AB Oxidized low density lipoprotein (oxLDL) induces apoptosis in vascular cells. To elucidate the mechanisms involved in this apoptosis, we studied the apoptosis-inducing activity in lipid fractions of oxLDL and the roles of two common mechanisms, **ceramide** generation and the activation of caspases, in apoptosis in human umbilical **vein** endothelial cells **treated** with oxLDL. We also studied the effects of antioxidants and cholesterol. oxLDL induced endothelial apoptosis in a time- and dose-dependent fashion. Apoptosis-inducing activity was recovered in the neutral lipid fraction of oxLDL. Various oxysterols in this fraction induced endothelial apoptosis. Neither the phospholipid fraction nor its component lysophosphatidylcholine **induced** apoptosis. oxLDL **induced ceramide** accumulation temporarily at 15 min in a dose-dependent fashion. Two **inhibitors** of acid sphinogomyelinase **inhibited** both the increase in **ceramide** and the apoptosis **induced** by oxLDL. Furthermore, a membrane-permeable **ceramide** (C2-**ceramide**) **induced** endothelial apoptosis. These findings demonstrated that **ceramide** generation by acid **sphingomyelinase** is indispensable for the endothelial apoptosis **induced** by oxLDL. Inhibitors of both caspase-1 and caspase-3 inhibited the apoptosis, suggesting that oxLDL induced apoptosis by activating these cysteine proteases. The antioxidants butylated hydroxytoluene and superoxide dismutase but not catalase inhibited the apoptosis induced by oxLDL or 25-hydroxycholesterol. This suggests not only that superoxide plays an important role but also that a critical interaction between oxLDL and the cell takes place on the outer surface of the membrane, because superoxide dismutase is not membrane-permeable. Exogenous cholesterol also inhibited the apoptosis. Our study demonstrated that neutral lipids in oxLDL **induce** endothelial apoptosis by activating membrane **sphingomyelinase** in a superoxide-dependent manner, as well as by activating caspases.

CT *Antioxidants: PD, pharmacology
Apoptosis: DE, drug effects
*Apoptosis: PH, physiology
Butylated Hydroxytoluene: PD, pharmacology
Catalase: PD, pharmacology
Cells, Cultured
Ceramides: ME, metabolism
Cholesterol: AA, analogs & derivatives
*Cholesterol: PD, pharmacology
Cysteine Endopeptidases: BI, biosynthesis
Cysteine Proteinase Inhibitors: PD, pharmacology
Endothelium, Vascular: CY, cytology
***Endothelium, Vascular: DE, drug effects**
Endothelium, Vascular: PH, physiology
Enzyme Activation
Fibroblast Growth Factor 2: PD, pharmacology
Humans
Kinetics
*Lipoproteins, LDL: PD, pharmacology
Oxidation-Reduction
Research Support, Non-U.S. Gov't
Sphingosine: AA, analogs & derivatives
Sphingosine: PD, pharmacology
*Sterols: PD, pharmacology
Superoxide Dismutase: PD, pharmacology
Umbilical Veins
RN 103107-01-3 (Fibroblast Growth Factor 2); **123-78-4 (Sphingosine)** ; 128-37-0 (Butylated Hydroxytoluene); 57-88-5 (Cholesterol)
CN 0 (Antioxidants); 0 (Ceramides); 0 (Cysteine Proteinase Inhibitors); 0 (Lipoproteins, LDL); 0 (N-acetylsphingosine); 0 (Sterols); 0 (oxidized low density lipoprotein); EC 1.11.1.6 (Catalase); EC 1.15.1.1 (Superoxide Dismutase); EC 3.4.22 (Cysteine Endopeptidases)

L161 ANSWER 61 OF 127 MEDLINE on STN
ACCESSION NUMBER: 1998250515 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9590633
TITLE: Cycloserine-**induced** decrease of **cerebroside** in myelin.
AUTHOR: Miller S L; Denisova L
CORPORATE SOURCE: Children's Hospital of Philadelphia and Department of Neurology, University of Pennsylvania School of Medicine, 19104, USA.
CONTRACT NUMBER: NS26844 (NINDS)
SOURCE: Lipids, **(1998 Apr)** Vol. 33, No. 4, pp. 441-3. Journal code: 0060450. ISSN: 0024-4201.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 23 Jul 1998
Last Updated on STN: 23 Jul 1998
Entered Medline: 10 Jul 1998
ED Entered STN: 23 Jul 1998
Last Updated on STN: 23 Jul 1998
Entered Medline: 10 Jul 1998
AB L-Cycloserine has been shown specifically to lower brain **cerebroside** levels in vivo, but the extent to which the decrease in whole brain **cerebroside** content reflects lower myelin **cerebroside** levels is not known since a substantial portion of

cerebroside is found in nonmyelin membranes. The present report demonstrates that chronically **administered** cycloserine lowers the proportion of **cerebroside** in rat **brain** myelin. Cycloserine-**induced** decrease of myelin **cerebroside** should provide a useful tool in investigating the role of **cerebroside** in maintaining myelin stability.

CT Check Tags: Female
Animals
Antibiotics, Antitubercular: AD, administration & dosage
*Antibiotics, Antitubercular: PD, pharmacology
Body Weight: DE, drug effects
*Brain: AH, anatomy & histology
Brain: DE, drug effects
Brain: ME, metabolism
Brain Chemistry: DE, drug effects
Cycloserine: AD, administration & dosage
*Cycloserine: PD, pharmacology
***Galactosylceramides: ME, metabolism**
*Myelin Sheath: CH, chemistry
*Myelin Sheath: DE, drug effects
Myelin Sheath: ME, metabolism
Organ Size: DE, drug effects
Phospholipids: ME, metabolism
Proteins: DE, drug effects
Proteins: ME, metabolism
Rats
Rats, Wistar
Research Support, U.S. Gov't, P.H.S.

RN 68-41-7 (Cycloserine)

CN 0 (Antibiotics, Antitubercular); 0 (Galactosylceramides); 0 (Phospholipids); 0 (Proteins)

L161 ANSWER 62 OF 127 MEDLINE on STN
ACCESSION NUMBER: 1999015258 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9798524
TITLE: Beneficial **effects** of N,N,N-**trimethylsphingosine** following ischemia and reperfusion in the isolated perfused rat heart.
AUTHOR: Campbell B; Shin Y K; Scalia R; Lefer A M
CORPORATE SOURCE: Department of Physiology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA 19107, USA.
CONTRACT NUMBER: GM-45434 (NIGMS)
SOURCE: Cardiovascular research, **(1998 Aug)** Vol. 39, No. 2, pp. 393-400.
Journal code: 0077427. ISSN: 0008-6363.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 15 Jan 1999
Last Updated on STN: 15 Jan 1999
Entered Medline: 8 Dec 1998

ED Entered STN: 15 Jan 1999
Last Updated on STN: 15 Jan 1999
Entered Medline: 8 Dec 1998

AB OBJECTIVE: Ischemia followed by reperfusion in the presence of polymorphonuclear leukocytes (PMNs) results in cardiac contractile dysfunction as well as myocardial injury. These deleterious effects are due in large part to endothelial dysfunction leading to an upregulation of

cell adhesion molecules and subsequent neutrophil-induced cardiac injury. At physiologically relevant concentrations, N,N,N-**trimethylsphingosine** (TMS), a synthetic N-methylated **sphingosine** derivative, has been shown to attenuate leukocyte-endothelial cell interactions. We wanted to test the effects of TMS on neutrophil-mediated cardiac dysfunction in ischemia/reperfusion. METHODS: This study examines the effects of TMS in a neutrophil-dependent isolated perfused rat heart model of ischemia (I) (20 min) and reperfusion (R) (45 min) injury. RESULTS: **Administration** of TMS (20 micrograms/kg) to I/R **hearts** perfused with PMNs improved coronary flow and preserved left ventricular developed pressure as an index of cardiac contractile function (95 +/- 5%) in comparison to those I/R hearts receiving only vehicle (60 +/- 7%) (P < 0.001). In addition, TMS significantly reduced PMN accumulation in the ischemic myocardium, as evidenced by an attenuation in cardiac myeloperoxidase activity from 1.12 +/- 0.04 in untreated **hearts** to 0.01 +/- 0.02 in **treated hearts** (P < 0.001). However, TMS did not directly stimulate nitric oxide (NO) release from rat vascular endothelium. CONCLUSION: These results provide evidence that TMS is a potent and effective cardioprotective agent that inhibits leukocyte-endothelial cell interactions and preserves cardiac contractile function and coronary perfusion following myocardial ischemia and reperfusion.

CT Check Tags: Male
Animals
Aorta
Disease Models, Animal
Electrodes
Endothelium, Vascular: DE, drug effects
Endothelium, Vascular: IM, immunology
Endothelium, Vascular: ME, metabolism
Enzyme Inhibitors: PD, pharmacology
*Enzyme Inhibitors: TU, therapeutic use
In Vitro
***Myocardial Contraction: DE, drug effects**
***Myocardial Reperfusion Injury: DT, drug therapy**
Myocardial Reperfusion Injury: IM, immunology
Myocardium: EN, enzymology
Myocardium: IM, immunology
Myocardium: ME, metabolism
Neutrophils: PH, physiology
Nitric Oxide: BI, biosynthesis
Perfusion
Peroxidase: ME, metabolism
*Protein Kinase C: AI, antagonists & inhibitors
Protein Kinase C: PD, pharmacology
Rats
Rats, Sprague-Dawley
Research Support, U.S. Gov't, P.H.S.
***Sphingosine: AA, analogs & derivatives**
Sphingosine: PD, pharmacology
Sphingosine: TU, therapeutic use
Ventricular Function, Left: DE, drug effects

RN 10102-43-9 (Nitric Oxide); **123-78-4 (Sphingosine)**; 138686-73-4 (N,N,N-trimethylsphingosine)

CN 0 (Enzyme Inhibitors); EC 1.11.1.7 (Peroxidase); EC 2.7.1.37 (Protein Kinase C)

L161 ANSWER 63 OF 127 MEDLINE on STN
ACCESSION NUMBER: 97281836 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9136132

TITLE: Effects of fumonisin B1 **treatment** on blood-**brain** barrier transfer in developing rats.
AUTHOR: Kwon O S; Sandberg J A; Slikker W Jr
CORPORATE SOURCE: Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, Little Rock 72205, USA.
SOURCE: Neurotoxicology and teratology, **(1997 Mar-Apr)** Vol. 19, No. 2, pp. 151-5.
Journal code: 8709538. ISSN: 0892-0362.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 9 Jul 1997
Last Updated on STN: 9 Jul 1997
Entered Medline: 23 Jun 1997
ED Entered STN: 9 Jul 1997
Last Updated on STN: 9 Jul 1997
Entered Medline: 23 Jun 1997
AB Fumonisin B1 (FB1), a toxic metabolite of the fungus Fusarium moniliforme found in contaminated corn, is considered an etiologic agent of equine leukoencephalomalacia. Because FB1 exposure is associated with alteration of sphingolipid metabolism, the purpose of this study was to elucidate whether blood sphinganine (Sa) levels affect brain Sa levels. Sa and sphingosine (So) levels in brain tissue and plasma were analyzed by HPLC. Area under the curve (AUC0-20h) ratios of brain Sa to plasma Sa levels were about 40 after a single 0.8 or 8 mg/kg SC dose of FB1. The AUC0-12h ratio of brain FB1 to plasma FB1 was 0.02. The fact that FB1 **alters** brain Sa levels and Sa/So ratios indicates that **sphingolipid** metabolism in the central nervous system of developing rats is vulnerable to FB1 exposure. These data support our hypothesis that alterations of the brain Sa levels are related to the direct action of FB1 on the brain rather than transport of peripheral Sa to the brain.
CT Check Tags: Female; Male
Animals
Area Under Curve
***Blood-Brain Barrier: DE, drug effects**
Blood-Brain Barrier: PH, physiology
Carboxylic Acids: BL, blood
*Carboxylic Acids: TO, toxicity
Carcinogens, Environmental: AN, analysis
*Carcinogens, Environmental: TO, toxicity
Chromatography, High Pressure Liquid
*Fumonisins
Pregnancy
Prosencephalon: CH, chemistry
Rats
Rats, Sprague-Dawley
***Sphingosine: AA, analogs & derivatives**
Sphingosine: BL, blood
Sphingosine: PK, pharmacokinetics
RN 116355-83-0 (fumonisin B1); **123-78-4 (Sphingosine)**; **764-22-7 (safingol)**
CN 0 (Carboxylic Acids); 0 (Carcinogens, Environmental); 0 (Fumonisins)

L161 ANSWER 64 OF 127 MEDLINE on STN
ACCESSION NUMBER: 96208873 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8627068
TITLE: Comparison of the effects of Shiga-like toxin 1 on

cytokine- and butyrate-**treated** human umbilical and saphenous **vein** endothelial cells.

AUTHOR: Keusch G T; Acheson D W; Aaldering L; Erban J; Jacewicz M S
CORPORATE SOURCE: Tupper Research Institute, Division of Geographic Medicine and Infectious Diseases, New England Medical Center, Boston, Massachusetts 02111, USA.
CONTRACT NUMBER: AI-07329 (NIAID)
AI-14242 (NIAID)
DK-34928 (NIDDK)
SOURCE: The Journal of infectious diseases, **(1996 May)** Vol. 173, No. 5, pp. 1164-70.
Journal code: 0413675. ISSN: 0022-1899.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199606
ENTRY DATE: Entered STN: 8 Jul 1996
Last Updated on STN: 29 Jan 1999
Entered Medline: 21 Jun 1996
ED Entered STN: 8 Jul 1996
Last Updated on STN: 29 Jan 1999
Entered Medline: 21 Jun 1996

AB To examine the reported heterogeneity of endothelial cells to Shiga-like toxin 1 (Stx1), the responses of human umbilical (HUVEC) and saphenous (HSVEC) vein endothelial cells to cytokines, butyrate, and toxin were compared. Untreated HSVEC were generally more susceptible than were HUVEC to Stx1; pretreatment of either cell with lipopolysaccharide, interleukin-1 beta, or tumor necrosis factor-alpha enhanced Stx1 toxicity. Dexamethasone alone increased total **globotriaosylceramide** (Gb3) content and toxin binding but **inhibited** cytokine-**enhanced** cytotoxicity, whereas the differentiation agent, sodium butyrate, increased both Gb3 content and cytotoxicity responses to Stx1, most prominently in HSVEC. Stx1 toxicity directly correlated with the release of von Willebrand factor from HSVEC but not from HUVEC. Thus, HUVEC and HSVEC exhibit distinctive responses to Stx1, cytokines, and butyrate. This suggests the need for caution in extrapolating from in vitro studies utilizing one endothelial cell type to in vivo events during pathogenesis of Stx-mediated thrombotic microangiopathies.

CT Bacterial Toxins: ME, metabolism
*Bacterial Toxins: TO, toxicity
Butyric Acid
*Butyric Acids: PD, pharmacology
Cells, Cultured
Comparative Study
*Cytokines: PD, pharmacology
Cytotoxins: ME, metabolism
*Cytotoxins: TO, toxicity
Dexamethasone: PD, pharmacology
Endothelium, Vascular: CH, chemistry
*Endothelium, Vascular: CY, cytology
Endothelium, Vascular: DE, drug effects
Humans
Interleukin-1: PD, pharmacology
Lipopolysaccharides: PD, pharmacology
Receptors, Cell Surface: AN, analysis
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
Saphenous Vein
Shiga-Like Toxin I

Sialoglycoproteins: PD, pharmacology
Tetradecanoylphorbol Acetate: PD, pharmacology
Trihexosylceramides: AN, analysis
Tumor Necrosis Factor-alpha: PD, pharmacology
Umbilical Veins
von Willebrand Factor: AN, analysis
RN 107-92-6 (Butyric Acid); 16561-29-8 (Tetradecanoylphorbol Acetate); 50-02-2 (Dexamethasone); 71965-57-6 (globotriaosylceramide)
CN 0 (Bacterial Toxins); 0 (Butyric Acids); 0 (Cytokines); 0 (Cytotoxins); 0 (Interleukin-1); 0 (Lipopolysaccharides); 0 (Receptors, Cell Surface); 0 (Shiga-Like Toxin I); 0 (Sialoglycoproteins); 0 (Trihexosylceramides); 0 (Tumor Necrosis Factor-alpha); 0 (interleukin 1 receptor antagonist protein); 0 (von Willebrand Factor)

L161 ANSWER 65 OF 127 MEDLINE on STN
ACCESSION NUMBER: 93375709 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7690100
TITLE: **Reduction** of myocardial ischemic reperfusion injury by sialylated **glycosphingolipids**, gangliosides.
AUTHOR: Maulik N; Das D K; Gogineni M; Cordis G A; Avrova N; Denisova N
CORPORATE SOURCE: Department of Surgery, University of Connecticut School of Medicine, Farmington 06030-1110.
CONTRACT NUMBER: HL 22559 (NHLBI)
HL 33889 (NHLBI)
HL 34360 (NHLBI)
SOURCE: Journal of cardiovascular pharmacology, **(1993 Jul)** Vol. 22, No. 1, pp. 74-81.
Journal code: 7902492. ISSN: 0160-2446.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199310
ENTRY DATE: Entered STN: 22 Oct 1993
Last Updated on STN: 3 Feb 1997
Entered Medline: 7 Oct 1993
ED Entered STN: 22 Oct 1993
Last Updated on STN: 3 Feb 1997
Entered Medline: 7 Oct 1993
AB Gangliosides, sialic acid-containing glycosphigolipids, are localized mostly to the outer leaflet of the lipid bilayer in the plasma membrane, particularly in brain. Gangliosides reduce edema formation, restore glucose metabolism, and increase cerebral blood flow after focal ischemia in the rat brain. We wished to determine whether gangliosides could also reduce myocardial ischemic and reperfusion injury. Isolated rat heart perfused by Langendorff technique was pretreated with gangliosides (1 microM) purified from the rat brain. After 15-min perfusion with gangliosides, hearts were made ischemic for 30 min by termination of coronary flow, followed by 60-min reperfusion. Ganglioside-**treated heart** exhibited better **myocardial** preservation, as evidenced by reduction in creatine kinase release and lipid peroxidation product formation enhanced coronary flow and contractile functions [left ventricular developed pressure (LVDP) and maximum first derivative of LVDP, LVdp/dtmax]. In addition, gangliosides reduced the hydroxyl radical formed during reperfusion of ischemic myocardium, as shown by high-performance liquid chromatography (HPLC)-electrochemical detection technique. In vitro studies demonstrated that these gangliosides were direct scavengers of superoxide anions (IC50

0.8 microM), and hydroxyl radicals (IC50 10 microM), as well hypohalite radicals (IC50 0.7 microM). Furthermore, ganglioside pretreatment was accompanied by reduced intracellular calcium overloading during ischemia and reperfusion as compared with untreated controls. The results of this study thus suggest that gangliosides can reduce ischemic reperfusion injury in isolated heart, probably by inhibiting intracellular calcium overloading and/or by directly scavenging the free radicals generated during reperfusion of ischemic myocardium.

CT Check Tags: Male
Animals
Coronary Circulation: DE, drug effects
Creatine Kinase: DE, drug effects
Free Radical Scavengers
***Gangliosides: PD, pharmacology**
Glycosphingolipids: CH, chemistry
***Glycosphingolipids: PD, pharmacology**
Hydroxides
Hydroxyl Radical
In Vitro
Malondialdehyde: ME, metabolism
*Myocardial Reperfusion Injury: PC, prevention & control
N-Acetylneuraminic Acid
Rats
Rats, Sprague-Dawley
Research Support, U.S. Gov't, P.H.S.
*Sialic Acids
Ventricular Function, Left: DE, drug effects

RN 131-48-6 (N-Acetylneuraminic Acid); 3352-57-6 (Hydroxyl Radical); 542-78-9 (Malondialdehyde)

CN 0 (Free Radical Scavengers); 0 (Gangliosides); 0 (Glycosphingolipids); 0 (Hydroxides); 0 (Sialic Acids); EC 2.7.3.2 (Creatine Kinase)

L161 ANSWER 66 OF 127 MEDLINE on STN
ACCESSION NUMBER: 89262456 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2725825
TITLE: The long-term **administration** of L-cycloserine to mice: specific **reduction** of **cerebroside** level.
AUTHOR: Sundaram K S; Lev M
CORPORATE SOURCE: Dept. of Microbiology, CUNY Medical School, NY 10031.
SOURCE: Neurochemical research, **(1989 Mar)** Vol. 14, No. 3, pp. 245-8.
Journal code: 7613461. ISSN: 0364-3190.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198906
ENTRY DATE: Entered STN: 9 Mar 1990
Last Updated on STN: 29 Jan 1999
Entered Medline: 23 Jun 1989

ED Entered STN: 9 Mar 1990
Last Updated on STN: 29 Jan 1999
Entered Medline: 23 Jun 1989

AB Short-term experiments in which L-cycloserine, the inhibitor of 3-ketodihydrosphinogosine synthase, was injected subcutaneously in young mice have shown that **cerebroside** synthesis is **inhibited** specifically. Studies on the **effect** of long term L-cycloserine **treatment** on **sphingolipid** synthesis were performed to determine whether mice could tolerate continued **cerebroside**

reduction and whether or not the synthesis of other **sphingolipids** would be **inhibited.** L-cycloserine, when injected at a low dose for a period of two months resulted in significantly **reduced** brain **cerebroside** level with little or no **reduction** in sulfatide, ganglioside, or **sphingomyelin** levels; liver and spleen glucocerebroside levels were also significantly **reduced.** The rate of **cerebroside** synthesis in brain was greatly **reduced,** whereas synthesis of sulfatides was much less affected by L-cycloserine indicating that a portion of newly synthesized galactocerebroside is shunted to synthesis of sulfatides.

CT Check Tags: Male
Animals
Brain: DE, drug effects
*Brain: ME, metabolism
***Cerebrosides: ME, metabolism**
*Cycloserine: AD, administration & dosage
Glycolipids: ME, metabolism
Mice
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, Non-P.H.S.
Sphingolipids: ME, metabolism
Sulfoglycosphingolipids: ME, metabolism

RN 68-41-7 (Cycloserine)
CN 0 (Cerebrosides); 0 (Glycolipids); 0 (Sphingolipids); 0 (Sulfoglycosphingolipids)

L161 ANSWER 67 OF 127 MEDLINE on STN
ACCESSION NUMBER: 89198852 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3241123
TITLE: Warfarin **administration reduces** synthesis of sulfatides and other **sphingolipids** in mouse **brain.**
AUTHOR: Sundaram K S; Lev M
CORPORATE SOURCE: CUNY Medical School, NY 10031.
SOURCE: Journal of lipid research, **(1988 Nov)** Vol. 29, No. 11, pp. 1475-9.
Journal code: 0376606. ISSN: 0022-2275.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198905
ENTRY DATE: Entered STN: 6 Mar 1990
Last Updated on STN: 29 Jan 1999
Entered Medline: 22 May 1989

ED Entered STN: 6 Mar 1990
Last Updated on STN: 29 Jan 1999
Entered Medline: 22 May 1989

AB The **modulation** of **phosphosphingolipid** synthesis by vitamin K depletion has been observed in the vitamin K-dependent microorganism, Bacteriodes levii. When cultured briefly without the vitamin, a **reduction** occurred in the activity of the first enzyme of the **sphingolipid** pathway, 3-**ketodihydrosphingosine** synthase. In this report, 16-day-old mice were **treated** with the vitamin K antagonist, warfarin. Brain microsomes from these animals showed a 19% reduction in synthase activity. Mice **treated** with warfarin for 2 weeks showed a major reduction in sulfatide level (42%), with a lesser degree or no **reduction** in levels of gangliosides and **cerebrosides.** In further

experiments, mice were **treated** with warfarin for 2 weeks and a group was then injected with vitamin K1 (aquamephyton) for 3 days. Enzyme activity returned to a normal level within 2-3 days. Sulfatide levels had increased 33% in the vitamin K-injected group and ganglioside levels also increased, where levels of **cerebrosides** and **sphingomyelin** declined. Sulfatide synthesis determined by [35S] sulfate incorporation, showed a 52% increase in incorporation following **administration** of vitamin K for 3 days. These results suggest a role for vitamin K in the biosynthesis of sulfatides and other **sphingolipids** in brain. This putative role could be by post-translational protein modification analogous to the role of vitamin K in other systems.

CT Animals
Brain: DE, drug effects
Brain: EN, enzymology
*Brain: ME, metabolism
Glycosphingolipids: BI, biosynthesis
Mice
Mice, Inbred ICR
Oxo-Acid-Lyases: ME, metabolism
Phospholipids: BI, biosynthesis
Research Support, U.S. Gov't, Non-P.H.S.
***Sphingolipids: BI, biosynthesis**
***Sulfoglycosphingolipids: BI, biosynthesis**
Vitamin K: AD, administration & dosage
Vitamin K: PH, physiology
Vitamin K Deficiency: ME, metabolism
*Warfarin: AD, administration & dosage

RN 12001-79-5 (Vitamin K); 81-81-2 (Warfarin)

CN 0 (Glycosphingolipids); 0 (Phospholipids); 0 (Sphingolipids); 0 (Sulfoglycosphingolipids); EC 4.1.3. (Oxo-Acid-Lyases); EC 4.1.3.- (3-ketodihydrosphingosine synthetase)

L161 ANSWER 68 OF 127 MEDLINE on STN
ACCESSION NUMBER: 87231985 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2884662
TITLE: Hematopoietic cell transplantation in murine globoid cell leukodystrophy (the twitcher mouse): **effects** on levels of **galactosylceramidase**, psychosine, and galactocerebrosides.
AUTHOR: Ichioka T; Kishimoto Y; Brennan S; Santos G W; Yeager A M
CONTRACT NUMBER: NS 13559 (NINDS)
NS 13569 (NINDS)
PO1 CA15396 (NCI)
+
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, **(1987 Jun)** Vol. 84, No. 12, pp. 4259-63.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198707
ENTRY DATE: Entered STN: 5 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 17 Jul 1987

ED Entered STN: 5 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 17 Jul 1987

AB Hematopoietic cell transplantation (HCT) prolongs survival in the twitcher mouse, an authentic animal model of human globoid cell leukodystrophy (Krabbe disease; **galactosylceramidase** deficiency), but the **effects** of HCT on levels of **galactosylceramidase**, psychosine, and **cerebrosides** in the tissues of twitcher mice have not been previously studied. **Galactosylceramidase** was less than 8% of **control** activity in tissues of untreated twitcher mice but reached normal values in brain and spleen and 20-30% of control in kidney of 100-day-old twitchers that received HCT at age 10 days. Using a recently developed method for the simultaneous determination of psychosine and cerebrosides, we measured the tissue levels of these lipids in the above animals. The levels of psychosine in brain, sciatic nerve, and kidney of untreated twitcher mice were 44, 200, and 12 times control values, respectively, in 30-day-old animals and 69, 500, and 14 times control levels in 40-day-old mice. On the other hand, levels of **cerebroside** were approximately 35% of **control** values in sciatic nerve, remained about the same in the brain, and were elevated 10-fold in the kidney of twitcher mice. After HCT, psychosine levels in the brains of 30-day-old twitchers were lowered to 30-35% of values in untreated twitchers, and the levels remained in that range during the post-HCT period. Similarly, **brain cerebroside** levels remained low in HCT-**treated** twitcher mice. Although psychosine levels in sciatic nerves of HCT-treated twitcher mice increased more slowly than in the nerves of untreated twitchers, the levels in 100-day-old HCT-treated twitcher mice had reached the same high values as those seen in untreated 40-day-old twitchers. It is not known whether the extremely high levels of psychosine in sciatic nerves ultimately contribute to the death of twitcher mice after HCT.

CT Aging
Animals
Brain: GD, growth & development
*Brain: ME, metabolism
***Cerebrosides: ME, metabolism**
Disease Models, Animal
*Galactosidases: ME, metabolism
*Galactosylceramidase: ME, metabolism
***Galactosylceramides: ME, metabolism**
*Hematopoietic Stem Cell Transplantation
Kidney: GD, growth & development
Kidney: ME, metabolism
Leukodystrophy, Globoid Cell: ME, metabolism
*Leukodystrophy, Globoid Cell: TH, therapy
Mice
Mice, Inbred C57BL
Mice, Neurologic Mutants
***Psychosine: ME, metabolism**
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, Non-P.H.S.
Research Support, U.S. Gov't, P.H.S.
Sciatic Nerve: GD, growth & development
*Sciatic Nerve: ME, metabolism
*Sphingosine: AA, analogs & derivatives

RN **123-78-4 (Sphingosine)**; 2238-90-6 (Psychosine)

CN 0 (Cerebrosides); 0 (Galactosylceramides); EC 3.2.1.- (Galactosidases); EC 3.2.1.46 (Galactosylceramidase)

L161 ANSWER 69 OF 127 MEDLINE on STN
ACCESSION NUMBER: 85253164 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2410058
TITLE: [Contractile capacity of isolated flaps from the aorta of

rats with stable **arterial** hypertension **caused** by the prolonged **administration** of **cerebrosides**].
Sokratitel'naia sposobnost' izolirovannykh loskutov iz aorty krys so stoikoi arterial'noi gipertenziei, vyzvannoi dlitel'nym vvedeniem tserebrozidov.
AUTHOR: Mirzoian S A; Sotskii O P; Sekoian E S; Topchian A V; Sarkisova G M
SOURCE: Biulleten' eksperimental'noi biologii i meditsiny, **(1985 Jun)** Vol. 99, No. 6, pp. 706-8.
Journal code: 0370627. ISSN: 0365-9615.
PUB. COUNTRY: USSR
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Russian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198508
ENTRY DATE: Entered STN: 20 Mar 1990
Last Updated on STN: 20 Mar 1990
Entered Medline: 29 Aug 1985
ED Entered STN: 20 Mar 1990
Last Updated on STN: 20 Mar 1990
Entered Medline: 29 Aug 1985
AB A study was made of the contractility of smooth muscle cells of abdominal aorta strips of noninbred white rats with stable arterial hypertension **induced** by protracted intraperitoneal injection of **cerebrosides** isolated from cattle brain. It was demonstrated that as compared with normotensive animals, smooth muscle cells of the animals' arteries are characterized by the increased influx of extracellular calcium via slow potential-dependent calcium channels and hypersensitivity to noradrenaline and serotonin.
CT Check Tags: Female
Animals
Aorta, Abdominal: DE, drug effects
Calcium: ME, metabolism
Cattle
***Cerebrosides: PD, pharmacology**
Comparative Study
English Abstract
*Hypertension: CI, chemically induced
Hypertension: PP, physiopathology
Ion Channels: DE, drug effects
*Muscle Contraction: DE, drug effects
***Muscle, Smooth, Vascular: DE, drug effects**
Rats
Time Factors
RN 7440-70-2 (Calcium)
CN 0 (Cerebrosides); 0 (Ion Channels)

L161 ANSWER 70 OF 127 MEDLINE on STN
ACCESSION NUMBER: 85236025 MEDLINE
DOCUMENT NUMBER: PubMed ID: 4009064
TITLE: **Inhibition** of **cerebroside** synthesis in the **brains** of mice **treated** with L-cycloserine.
AUTHOR: Sundaram K S; Lev M
SOURCE: Journal of lipid research, **(1985 Apr)** Vol. 26, No. 4, pp. 473-7.
Journal code: 0376606. ISSN: 0022-2275.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198507
ENTRY DATE: Entered STN: 20 Mar 1990
Last Updated on STN: 6 Feb 1998
Entered Medline: 31 Jul 1985
ED Entered STN: 20 Mar 1990
Last Updated on STN: 6 Feb 1998
Entered Medline: 31 Jul 1985
AB Subcutaneous injection of L-cycloserine resulted in a 28% **reduction** in **cerebroside** levels in mouse brain but had no **effect** on the levels of gangliosides. In contrast, intraperitoneal injection results in a **reduction** of ganglioside as well as **cerebroside** + sulfatide levels. The route of injection influenced the degree of 3-**ketodihydrosphingosine** synthase **inhibition.** Intraperitoneal injection caused a rapid decrease in synthase activity followed by recovery over 48 hr, whereas subcutaneous injection resulted in no inhibition over this time; only after daily injection for a week was synthase activity reduced 35%. One week following cessation of L-cycloserine **administration**, enzyme activity had recovered, whereas the **cerebroside** level continued to fall. All lipids and enzymes showed normal levels 3 weeks post-cycloserine **administration.** L-[3H]serine incorporation into glycolipids showed that **cerebroside** synthesis was most affected, whereas sulfatide synthesis was less affected. One week after cessation of cycloserine **treatment**, **cerebroside** synthesis was still severely **inhibited**, whereas sulfatide levels were near normal. Two weeks after cessation of L-cycloserine **administration**, synthesis of these glycolipids was similar to that of controls.
CT Check Tags: Male
Animals
Brain: DE, drug effects
*Brain: ME, metabolism
Cerebrosides: AI, antagonists & inhibitors
***Cerebrosides: BI, biosynthesis**
*Cycloserine: PD, pharmacology
Gangliosides: BI, biosynthesis
Glycolipids: BI, biosynthesis
Kinetics
Mice
Oxo-Acid-Lyases: ME, metabolism
Research Support, Non-U.S. Gov't
Tritium
RN 10028-17-8 (Tritium); 68-41-7 (Cycloserine)
CN 0 (Cerebrosides); 0 (Gangliosides); 0 (Glycolipids); EC 4.1.3. (Oxo-Acid-Lyases); EC 4.1.3.- (3-ketodihydrosphingosine synthetase)

L161 ANSWER 71 OF 127 MEDLINE on STN
ACCESSION NUMBER: 83076391 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6959686
TITLE: **Effect** of glucocorticoids on **galactosylceramide** sulfotransferase activity in rat brain.
AUTHOR: Meyer J S; Czupryna M
CONTRACT NUMBER: RR07048 (NCRR)
SOURCE: Brain research, **(1982 Dec 2)** Vol. 252, No. 1, pp. 192-6.
Journal code: 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198302
ENTRY DATE: Entered STN: 17 Mar 1990
Last Updated on STN: 29 Jan 1999
Entered Medline: 25 Feb 1983
ED Entered STN: 17 Mar 1990
Last Updated on STN: 29 Jan 1999
Entered Medline: 25 Feb 1983
AB Previous studies have shown that glucocorticoids can **induce** the sulfatide-forming enzyme **galactosylceramide** sulfotransferase (GalCer-ST) in cultured glioblastoma cells. To investigate whether a similar process occurs in vivo, we **administered** corticosterone to infant and adult adrenalectomized rats and then assayed **brain** GalCer-ST activity and sulfatide content. Both measures were unexpectedly decreased rather than increased by hormone **treatment**, indicating that glucocorticoids may not regulate **brain** sulfatide biosynthesis in the same manner as observed in clonal cell lines.
CT Check Tags: Female; Male
Adrenalectomy
Animals
***Brain: DE, drug effects**
Brain: EN, enzymology
*Corticosterone: PD, pharmacology
Myelin Sheath: DE, drug effects
Rats
Rats, Inbred Strains
Research Support, U.S. Gov't, P.H.S.
Sulfoglycosphingolipids: ME, metabolism
*Sulfotransferases
*Sulfurtransferases: ME, metabolism
RN 50-22-6 (Corticosterone)
CN 0 (Sulfoglycosphingolipids); EC 2.8.1 (Sulfurtransferases); EC 2.8.2 (Sulfotransferases); EC 2.8.2.11 (galactosylceramide sulfotransferase)

L161 ANSWER 72 OF 127 MEDLINE on STN
ACCESSION NUMBER: 81221176 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7017438
TITLE: Triethyllead **treatment** of cultured **brain** cells. Effect on accumulation of radioactive precursors in galactolipids.
AUTHOR: Grundt I K; Ammitzboll T; Clausen J
SOURCE: Neurochemical research, **(1981 Feb)** Vol. 6, No. 2, pp. 193-201.
Journal code: 7613461. ISSN: 0364-3190.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198108
ENTRY DATE: Entered STN: 16 Mar 1990
Last Updated on STN: 29 Jan 1999
Entered Medline: 20 Aug 1981
ED Entered STN: 16 Mar 1990
Last Updated on STN: 29 Jan 1999
Entered Medline: 20 Aug 1981
AB Cultured cells from chick embryo brains were studied for their sensitivity to triethyllead. Triethyllead chloride (3.16 microM) was added to the nutrient medium and incubated for 48 hr with the cells. Morphological

changes in light microscope and radioactive labeling of galactolipids were assayed. Triethyllead **treatment** reduced the number of neuronal cells with processes. Morphological changes were not observed in glial cells. The [35S]sulfate labeling of sulfatides was reduced to 50%. The [3H]serine labeling of **cerebrosides** with alpha-hydroxy fatty acids was not influenced, while the [3H]serine labeling of **cerebrosides** with nonhydroxy fatty acids was **inhibited** 40% in one- and two- but not in three-week-old cultures. The results indicate that the nerve cell response to triethyllead in cultures is selective, since the neurons are more sensitive than the glia cells and the labeling of sulfatides is more sensitive than that of **cerebrosides.**

CT Animals
Brain: DE, drug effects
*Brain: ME, metabolism
Cells, Cultured
Chick Embryo
Chromatography, Thin Layer
Galactolipids
*Glycolipids: BI, biosynthesis
*Lead: PD, pharmacology
*Organometallic Compounds: PD, pharmacology
Radioisotope Dilution Technique
Research Support, Non-U.S. Gov't
Sulfoglycosphingolipids: BI, biosynthesis
Sulfur Radioisotopes
Tritium

RN 10028-17-8 (Tritium); 5224-23-7 (triethyllead); 7439-92-1 (Lead)
CN 0 (Galactolipids); 0 (Glycolipids); 0 (Organometallic Compounds); 0 (Sulfoglycosphingolipids); 0 (Sulfur Radioisotopes)

L161 ANSWER 73 OF 127 MEDLINE on STN
ACCESSION NUMBER: 82032537 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7288511
TITLE: **Effect** of nicotinic acid on **cerebroside** synthesis in rat brain.
AUTHOR: Nakashima Y; Suzue R
SOURCE: Journal of nutritional science and vitaminology, **(1981)** Vol. 27, No. 1, pp. 23-31.
Journal code: 0402640. ISSN: 0301-4800.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198112
ENTRY DATE: Entered STN: 16 Mar 1990
Last Updated on STN: 16 Mar 1990
Entered Medline: 21 Dec 1981

ED Entered STN: 16 Mar 1990
Last Updated on STN: 16 Mar 1990
Entered Medline: 21 Dec 1981

AB The **effect** of nicotinic acid on the synthesis of **cerebrosides** in the brain was studied during brain development. The concentration of **cerebrosides** in the brain was significantly lower in nicotinic acid-deficient animals than in those receiving a nicotinic acid-supplemented diet. The total lipid concentration in the brain of nicotinic acid-deficient rats was slightly lower than that of rats fed on the nicotinic acid-supplemented diet. Therefore, the ratio of **cerebrosides** to total lipids of nicotinic acid-deficient rats was markedly lower than that of nicotinic acid-supplemented rats. However,

this low **cerebroside** level in nicotinic acid-deficient rats was restored by the **administration** of the nicotinic acid-supplemented diet. Synthesis of **cerebrosides** was followed in the brain of developing rats after intracerebral injection of L-[U]14C]serine. The total amount of radioactivity incorporated into the **cerebroside** fraction of nicotinic acid-deficient rat was smaller than that of nicotinic acid supplemented rats. These observations suggest that nicotinic acid affects **cerebroside** synthesis in the brain of rats.

CT Animals
Body Weight: DE, drug effects
***Brain: DE, drug effects**
Brain: GD, growth & development
Brain: ME, metabolism
***Cerebrosides: BI, biosynthesis**
Diet
Lipids: BI, biosynthesis
Niacin
Nicotinic Acids: DF, deficiency
*Nicotinic Acids: PD, pharmacology
Organ Size: DE, drug effects
Rats
Rats, Inbred Strains

RN 59-67-6 (Niacin)
CN 0 (Cerebrosides); 0 (Lipids); 0 (Nicotinic Acids)

L161 ANSWER 74 OF 127 MEDLINE on STN
ACCESSION NUMBER: 78234742 MEDLINE
DOCUMENT NUMBER: PubMed ID: 277123
TITLE: Toxicology of triethyllead, methylmercury and cadmium, determined in chick embryo brain cell cultures.
AUTHOR: Ammitzboll T; Kobayasi T; Grundt I; Clausen J
SOURCE: Archives of toxicology. Supplement. = Archiv fur Toxikologie. Supplement, **(1978)** No. 1, pp. 319-22.
Journal code: 7802567. ISSN: 0171-9750.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197809
ENTRY DATE: Entered STN: 14 Mar 1990
Last Updated on STN: 29 Jan 1999
Entered Medline: 25 Sep 1978

ED Entered STN: 14 Mar 1990
Last Updated on STN: 29 Jan 1999
Entered Medline: 25 Sep 1978

AB The toxicology of water soluble chemical compounds may be investigated in tissue culture systems. The toxicology of triethyllead chloride, methylmercury chloride and cadmium acetate was studied in chick embryo brain cell cutlures. Tetraethyllead is added to petrol as an anti-knock agent. When tetraethyllead is absorbed by the organism, it is converted to triethyllead which cause the symptoms of tetraethyllead poisoning. Chick embryo brain cell cultures derived from cerebrum of 11-day-old chick embryos developed both neurons and glial cells. The neurons formed nerve processes and synapsis in the cultures. The effect of triethyllead chloride was investigated by addition of triethyllead chloride to the nutrient medium. The median tissue culture lethal dose, TCLD50 = 1.9 mg/l, was determined as the concentration of triethyllead chloride at which the confluent layer of glial cells was destroyed in 50% of the

cultures. The neurons lost their processes at even lower concentration, TCED50 = 0.57 mg/l. Electron microscopy revealed cells with swollen Golgi apparatus and dilated endoplasmic reticulum in chick embryo **brain** cell cultures which were **treated** with triethyllead chloride, 1.0 mg/l. Studies with radioactive labelled precursors revealed that triethyllead chloride **inhibited** the synthesis of DNA, sulfatides and **cerebrosides** without hydroxyfatty acids.

CT Animals
Astrocytes: DE, drug effects
Brain: CY, cytology
***Brain: DE, drug effects**
Brain: ME, metabolism
*Cadmium: TO, toxicity
Cells, Cultured
Cerebrosides: BI, biosynthesis
Chick Embryo
DNA: BI, biosynthesis
*Lead: TO, toxicity
Lethal Dose 50
*Methylmercury Compounds: TO, toxicity
*Organometallic Compounds: TO, toxicity
Sulfoglycosphingolipids: BI, biosynthesis
Synapses: DE, drug effects

RN 7439-92-1 (Lead); 7440-43-9 (Cadmium); 9007-49-2 (DNA)
CN 0 (Cerebrosides); 0 (Methylmercury Compounds); 0 (Organometallic Compounds); 0 (Sulfoglycosphingolipids)

L161 ANSWER 75 OF 127 MEDLINE on STN
ACCESSION NUMBER: 77051310 MEDLINE
DOCUMENT NUMBER: PubMed ID: 993205
TITLE: C20-sphingosine as a determining factor in aggregation of gangliosides.
AUTHOR: Yohe H C; Roark D E; Rosenberg A
SOURCE: The Journal of biological chemistry, **(1976 Nov 25)** Vol. 251, No. 22, pp. 7083-7.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197701
ENTRY DATE: Entered STN: 13 Mar 1990
Last Updated on STN: 13 Mar 1990
Entered Medline: 29 Jan 1977

ED Entered STN: 13 Mar 1990
Last Updated on STN: 13 Mar 1990
Entered Medline: 29 Jan 1977

AB Aggregation properties of gangliosides, the major synaptic membrane **glycosphingolipids** of mammalian **brain**, may **prevent** their segregation during membrane assembly and promote a uniform membrane matrix with minimum maintenance energy. The sphingosine residues of bovine brain gangliosides show an increase in C20-sphingosine corresponding with an increase in sialic acid. Concentrations of C20-sphingosine varied from 37% for the monosialoganglioside to 64% for the trisialoganglioside, the remainder being C18-sphingosine. Ultracentrifugal analysis showed that changes in sialic acid content and in C20-sphingosine content individually affect micellar size. Increases in sialic acid content decreased micellar size from 225 for the monosialoganglioside to 120 monomersper micelle for the trisialoganglioside. Monosialogangliosides enzymatically prepared from

oligosialohomologues with a higher C20-**sphingosine** content gave evidence for a considerable **effect** of **C20sphingosine** upon the free energy of the aggregate form; the number of monomers per micelle increased from 225 for the natural monosialoganglioside to 280 for monosialoganglioside derived from trisialoganglioside. The similar aggregation energies of the major synaptic membrane gangliosides apparently result from a metabolic balancing of increased C20-sphingosine with increased sialic acid content.

CT Animals
Binding Sites
Brain Chemistry
Cattle
Chromatography, Gas
***Gangliosides**
Micelles
Molecular Weight
Oligosaccharides: AN, analysis
Research Support, U.S. Gov't, P.H.S.
*Sphingosine
Structure-Activity Relationship

RN **123-78-4 (Sphingosine)**
CN 0 (Gangliosides); 0 (Oligosaccharides)

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ACCESSION NUMBER: 1999182896 EMBASE
TITLE: **Therapeutic** strategies to reduce TNF-α mediated cardiac contractile depression following **ischemia** and reperfusion.
AUTHOR: Cain B.S.; Harken A.H.; Meldrum D.R.
CORPORATE SOURCE: D.R. Meldrum, Department of Surgery, C-320, Univ. Colorado Health Sciences Ctr., 4200 East Ninth Avenue, Denver, CO 80262, United States. danmeldrum@netscape.net
SOURCE: Journal of Molecular and Cellular Cardiology, (1999) Vol. 31, No. 5, pp. 931-947. .
Refs: 143
ISSN: 0022-2828 CODEN: JMCDAY
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 10 Jun 1999
Last Updated on STN: 10 Jun 1999

ED Entered STN: 10 Jun 1999
Last Updated on STN: 10 Jun 1999

AB **Therapeutic** Strategies to Reduce TNF-α Mediated Cardiac Contractile Depression Following **Ischemia** and Reperfusion. Recent evidence has implicated proinflammatory mediators such as TNF-α in the pathophysiology of ischemia-reperfusion (I/R) injury. Clinically, serum levels of TNF-α are increased after myocardial infarction and after cardiopulmonary bypass. Each of these represent clinically relevant instances of cardiac I/R injury. We and others have recently reported that TNF-α is produced by the heart following experimental I/R in animals and that TNF-α directly decreases animal and human myocardial contractility in a dose dependent fashion. Thus,

strategies to reduce or neutralize myocardial TNF-α production should conceptually decrease myocardial contractile dysfunction following I/R. The purposes of this manuscript are: 1) to explore the clinical and experimental instances of I/R injury in which TNF-α is elevated, 2) to review the molecular mechanisms of TNF-α induced contractile dysfunction, 3) to examine both experimental and clinical strategies of reducing myocardial TNF-α production, and 4) to determine the influence of reducing post-I/R TNF-α on cardiac contractile function in both animals and man.

CT Medical Descriptors:
*heart muscle contractility
*heart muscle ischemia
*heart muscle reperfusion
*reperfusion injury
review
priority journal
Drug Descriptors:
*tumor necrosis factor alpha: EC, endogenous compound
adenosine: DV, drug development
adenosine: PD, pharmacology
mitogen activated protein kinase: EC, endogenous compound
4 (4 fluorophenyl) 2 (4 methylsulfinylphenyl) 5 (4 pyridyl)imidazole: DV, drug development
4 (4 fluorophenyl) 2 (4 methylsulfinylphenyl) 5 (4 pyridyl)imidazole: PD, pharmacology
immunoglobulin enhancer binding protein: EC, endogenous compound
tumor necrosis factor alpha antibody: DV, drug development
tumor necrosis factor alpha antibody: PD, pharmacology
dexamethasone: DV, drug development
dexamethasone: PD, pharmacology
tumor necrosis factor alpha receptor: DV, drug development
tumor necrosis factor alpha receptor: PD, pharmacology
interleukin 1 receptor blocking agent: DV, drug development
interleukin 1 receptor blocking agent: PD, pharmacology
nitric oxide: EC, endogenous compound
nitric oxide synthase inhibitor: DV, drug development
nitric oxide synthase inhibitor: PD, pharmacology
n(g) nitroarginine methyl ester: DV, drug development
n(g) nitroarginine methyl ester: PD, pharmacology
sphingosine: EC, endogenous compound
ethanolamine derivative: DV, drug development
ethanolamine derivative: PD, pharmacology
phospholipase a2: EC, endogenous compound
mepacrine: DV, drug development
mepacrine: PD, pharmacology
lisofylline: DV, drug development
lisofylline: PD, pharmacology
phosphodiesterase inhibitor: DV, drug development
phosphodiesterase inhibitor: PD, pharmacology
piperanometozine: DV, drug development
piperanometozine: PD, pharmacology
amrinone: DV, drug development
amrinone: PD, pharmacology
milrinone: DV, drug development
milrinone: PD, pharmacology
pentoxifylline: DV, drug development
pentoxifylline: PD, pharmacology
antioxidant: DV, drug development
antioxidant: PD, pharmacology
acetylcysteine: DV, drug development

acetylcysteine: PD, pharmacology
allopurinol: DV, drug development
allopurinol: PD, pharmacology
deferoxamine: DV, drug development
deferoxamine: PD, pharmacology
cytokine: DV, drug development
cytokine: EC, endogenous compound
cytokine: PD, pharmacology
interleukin 10: DV, drug development
interleukin 10: PD, pharmacology
aprotinin: DV, drug development
aprotinin: PD, pharmacology
unindexed drug

RN (adenosine) 58-61-7; (mitogen activated protein kinase) 142243-02-5; (4 (4 fluorophenyl) 2 (4 methylsulfinylphenyl) 5 (4 pyridyl)imidazole) 152121-47-6; (dexamethasone) 50-02-2; (nitric oxide) 10102-43-9; (n(g) nitroarginine methyl ester) 50903-99-6; (**sphingosine**) **123-78-4**; (phospholipase a2) 9001-84-7; (mepacrine) 69-05-6, 83-89-6; (lisofylline) 100324-81-0, 151852-32-3, 6493-06-7; (piperanometozine) 81840-15-5; (amrinone) 60719-84-8; (milrinone) 78415-72-2; (pentoxifylline) 6493-05-6; (acetylcysteine) 616-91-1; (allopurinol) 315-30-0; (deferoxamine) 70-51-9; (aprotinin) 11004-21-0, 12407-79-3, 50936-63-5, 52229-70-6, 58591-29-0, 9050-74-2, 9075-10-9, 9087-70-1

CN Sb 203580; Quinacrine; Vesnarinone

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ACCESSION NUMBER: 2005351923 EMBASE
TITLE: Growth factors and gangliosides as neuroprotective agents in excitotoxicity and ischemia.
AUTHOR: Hicks D.; Heidinger V.; Mohand-Said S.; Sahel J.; Dreyfus H.
CORPORATE SOURCE: D. Hicks, Laboratoire de Physiopathologie Retinienne, INSERM CJF 92-02, Centre Hospitalier et Universitaire Regional, 1 Place de l'Hopital, 67091 Strasbourg Cedex, France. hicks@neurochem.u-strasbg.fr
SOURCE: Vascular Pharmacology, (1998) Vol. 30, No. 3, pp. 265-273.
.
Refs: 61
ISSN: 1537-1891 CODEN: VPAHAJ
PUBLISHER IDENT.: S 0306-3623(97)00356-X
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 008 Neurology and Neurosurgery
012 Ophthalmology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 1 Sep 2005
Last Updated on STN: 1 Sep 2005

ED Entered STN: 1 Sep 2005
Last Updated on STN: 1 Sep 2005

AB At least two different groups of molecules can be considered neurotrophic factors because they exert a variety of effects upon neural cells. The first consists of the numerous families of polypeptide growth factors known to take part in almost all stages of neural cell growth and functioning, including development, differentiation, survival and

pathology. The second group also is characterized by extensive complexity of multiple forms, and consists of the sialic acid-containing **glycosphingolipids** or gangliosides. These molecules also take part in the transfer of information from the extracellular milieu to the cell interior, and, similarly to growth factors, are participants in such aspects as development, differentiation and functioning. In this short overview, we consider the existing data on the neuroprotective effects of growth factors [e.g., basic fibroblast growth factor (bFGF), epidermal growth factor (EGF) and brain-derived neurotrophic factor] and one species of ganglioside (GM1) against retinal ischemia in vivo and cerebral excitotoxicity in vitro. We used three different experimental models to investigate their relevance to ischemic and excitotoxic conditions in the retina and have shown that: (a) both bFGF and EGF show highly effective neuroprotection for rat retinal neurons exposed to toxic levels of glutamate or its nonphysiological agonist kainate in vitro (b) retinal glial cells suffer morphological perturbations after glutamate or kainate treatment, and this effect depends on neuron-glial interactions; (c) these glial changes can also be corrected by posttreatment with either bFGF or EGF in vitro; (d) with the use of an in vivo animal model involving anterior chamber pressure-induced ischemia in adult rats, either pretreatment by intraperitoneal injection of GM1 or posttreatment by intraocular injection of the same ganglioside significantly reduces histological damage to inner nuclear regions. Hence both groups of trophic molecules show interesting features for retinal **ischemic treatment.** .COPYRGT. 1998 Elsevier Science Inc.

CT Medical Descriptors:
*neuroprotection
*excitotoxicity
*retina ischemia
in vivo study
in vitro study
experimental model
retina nerve cell
cell interaction
glia cell
drug megadose
side effect: SI, side effect
human
nonhuman
conference paper
priority journal
Drug Descriptors:
*growth factor: CM, drug comparison
*growth factor: PD, pharmacology
*ganglioside: AE, adverse drug reaction
*ganglioside: AD, drug administration
*ganglioside: DO, drug dose
*ganglioside: IO, intraocular drug administration
*ganglioside: IP, intraperitoneal drug administration
*ganglioside: VI, intravitreal drug administration
*ganglioside: PD, pharmacology
*neuroprotective agent: AE, adverse drug reaction
*neuroprotective agent: AD, drug administration
*neuroprotective agent: CM, drug comparison
*neuroprotective agent: DO, drug dose
*neuroprotective agent: IO, intraocular drug administration
*neuroprotective agent: IP, intraperitoneal drug administration
*neuroprotective agent: VI, intravitreal drug administration
*neuroprotective agent: PD, pharmacology
*basic fibroblast growth factor: CM, drug comparison

*basic fibroblast growth factor: PD, pharmacology
*epidermal growth factor: CM, drug comparison
*epidermal growth factor: PD, pharmacology
*brain derived neurotrophic factor: PD, pharmacology
glutamic acid
kainic acid
RN (basic fibroblast growth factor) 106096-93-9; (epidermal growth factor) 62229-50-9; (brain derived neurotrophic factor) 218441-99-7; (glutamic acid) 11070-68-1, 138-15-8, 56-86-0, 6899-05-4; (kainic acid) 487-79-6

L161 ANSWER 78 OF 127 EMBASE DUPLICATE 13
ACCESSION NUMBER: 94343839 EMBASE
DOCUMENT NUMBER: 1994343839
TITLE: Protection by prosaposin against ischemia-induced learning disability and neuronal loss.
AUTHOR: Sano A.; Matsuda S.; Wen T.-C.; Kotani Y.; Kondoh K.; Ueno S.; Kakimoto Y.; Yoshimura H.; Sakanaka M.
CORPORATE SOURCE: Department of Neuropsychiatry, Ehime University School of Medicine,Shigenobu, Onsen-gun, Ehime 791-02, Japan
SOURCE: Biochemical and Biophysical Research Communications, (1994) Vol. 204, No. 2, pp. 994-1000. .
ISSN: 0006-291X CODEN: BBRCA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
029 Clinical Biochemistry
032 Psychiatry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 7 Dec 1994
Last Updated on STN: 7 Dec 1994
ED Entered STN: 7 Dec 1994
Last Updated on STN: 7 Dec 1994
AB Prosaposin, the protein precursor of saposins A, B, C, and D which activate **sphingolipid** hydrolases, is abundant in several brain regions including the hippocampus. We infused prosaposin continuously for 7 days into the lateral ventricle of gerbils starting 3 hours before 3-min of forebrain ischemia. Using the step-down passive **avoidance** task, we demonstrated that **ischemia**-induced learning disability is **prevented** almost completely by prosaposin infusion. Subsequent light and electron microscopic examinations showed that pyramidal neurons in the CA1 field of the hippocampus as well as synapses within the strata moleculare, lacunosum/radiatum and oriens of the field were significantly more numerous in gerbils infused with prosaposin infusion than in those receiving saline infusion. These findings suggest that prosaposin possesses neurotrotrophic activity to protect hippocampal CA1 neurons from lethal ischemic damage.
CT Medical Descriptors:
*brain ischemia
*learning disorder: PC, prevention
animal experiment
animal tissue
article
avoidance behavior
controlled study
gerbil
hippocampus

intracerebroventricular drug administration
nerve cell
nonhuman
priority journal
Drug Descriptors:
*prosaposin: PD, pharmacology
*protein precursor
***sphingolipid activator protein: PD, pharmacology**

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ACCESSION NUMBER: 93260478 EMBASE
DOCUMENT NUMBER: 1993260478
TITLE: Protein kinases modulate the sensitivity of hippocampal neurons to nitric oxide toxicity and anoxia.
AUTHOR: Maiese K.; Boniece I.R.; Skurat K.; Wagner J.A.
CORPORATE SOURCE: Department of Neurology, Cornell University Medical College, 1300 York Avenue,New York, NY 10021, United States
SOURCE: Journal of Neuroscience Research, (1993) Vol. 36, No. 1, pp. 77-87. .
ISSN: 0360-4012 CODEN: JNREDK
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 3 Oct 1993
Last Updated on STN: 3 Oct 1993
ED Entered STN: 3 Oct 1993
Last Updated on STN: 3 Oct 1993

AB Multiple processes lead to neuronal death after ischemia, but the generation of nitric oxide (NO) is a key component in this cascade of events. The mechanisms that regulate the extent of neuronal degeneration during anoxia and NO toxicity are multifactorial. Neuronal death may be modulated by the activity of signal transduction systems that influence the toxicity of NO or its metabolic products such as cGMP. The enzyme responsible for the production of NO, nitric oxide synthase (NOS), is phosphorylated by protein kinase C (PKC), the cAMP-dependent protein kinase (PKA), and the calcium/calmodulin-dependent protein kinase II (CaM-II). We examined in primary cultured hippocampal neurons whether the protein kinases PKC, PKA, CaM-II, and cGMP-dependent protein kinase modified the toxic effects of anoxia and NO. Down-regulation of PKC activity with PMA (1 μM) increased hippocampal neuronal survival during anoxia and NO exposure from approximately 22% to 88%. **Inhibitors** of PKC activity (H-7, H-8, **sphingosine**, and staurosporine) also were neuroprotective. Down-regulation of PKC activity increased survival during anoxia even in the presence of the NOS inhibitor, N(ω)-methyl-L-arginine. Thus, although down-regulation of PKC activity may increase neuronal survival by decreasing NOS activity, it also is likely that PKC contributes to ischemic neuronal death by mechanisms that are independent of NOS. Inhibition of the cGMP-dependent protein kinase activity, but not the activity of the CaM-II also was neuroprotective during NO administration. In contrast to the protective effects of inhibition of PKC and the cGMP- dependent protein kinase, activation rather than inhibition of PKA increased hippocampal neuronal survival during NO exposure. These results indicate that neuronal survival during anoxia and NO exposure is linked to the modulation of PKC, PKA, and cGMP-dependent protein kinase activity but is not dependent on the CaM-II pathway. Understanding the involvement of PKC, PKA, and the

cGMP-dependent protein kinase in modulating the effect of neuronal death during **ischemia** and NO toxicity may help in directing future **therapeutic** modalities for cerebrovascular disease.

CT Medical Descriptors:
*anoxia
*brain ischemia
*brain protection
*neurotoxicity
animal cell
article
down regulation
enzyme activity
enzyme inhibition
enzyme regulation
hippocampus
nonhuman
priority journal
protein phosphorylation
rat
Drug Descriptors:
*cyclic amp dependent protein kinase
*cyclic gmp dependent protein kinase
*nitric oxide: TO, drug toxicity
*protein kinase c
nitric oxide synthase
protein kinase (calcium,calmodulin) ii

RN (nitric oxide) 10102-43-9; (protein kinase c) 141436-78-4; (nitric oxide synthase) 125978-95-2; (protein kinase (calcium,calmodulin) ii) 141467-21-2

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ACCESSION NUMBER: 92225061 EMBASE
DOCUMENT NUMBER: 1992225061
TITLE: Loss and recovery of activities of α+ and α isozymes of (Na+ + K+)- ATPase in cortical focal ischemia: GM1 ganglioside protects plasma membrane structure and function.
AUTHOR: Mahadik S.P.; Bharucha V.A.; Stadlin A.; Ortiz A.; Karpiak S.E.
CORPORATE SOURCE: Department of Psychiatry, Medical College of Georgia, 1515 Pope Ave.,Augusta, GA 30912, United States
SOURCE: Journal of Neuroscience Research, (1992) Vol. 32, No. 2, pp. 209-220. .
ISSN: 0360-4012 CODEN: JNREDK
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Aug 1992
Last Updated on STN: 16 Aug 1992

ED Entered STN: 16 Aug 1992
Last Updated on STN: 16 Aug 1992

AB Alterations in cellular membrane structure and the subsequent failure of its function after CNS ischemia were monitored by analyzing changes in the

plasma membrane marker enzyme (Na+ + K+)-ATPase. The levels of two isozymes of (Na+ + K+)-ATPase, α+ and α, which have distinct cellular and anatomical distributions, were studied to determine if differential cellular damage occurs in primary and peri-ischemic injury areas. The efficacy of monosialoganglioside (GM1) **treatment** was assessed, since this **glycosphingolipid** has been shown to **reduce ischemic** injury by protecting cell membrane structure/function. Using a rat model of cortical focal ischemia, levels of both ATPase isozyme activities were assayed in total membrane fractions from primary ischemic tissue (parietal cortex) and three peri- ischemic tissue areas (frontal, occipital, and temporal cortex) at 1, 3, 5, 7, and 14 days after ischemia. No significant loss of either isozyme's activity occurred in any tissue area at 1 day after ischemia. At 5 days, in the primary ischemic area, both isozyme activity levels decreased by 70-75%. The α+ enzyme activity loss persisted up to 14 days, while a 17% recovery in α activity occurred. In the three peri-ischemic tissue areas, enzyme activity losses ranged from 42%-59% at 3 days after ischemia. A complete restoration of both isozyme activities was seen at 14 days. After three days of GM1 ganglioside treatment there was no loss of total (Na+ + K+)-ATPase activity in the three peri-ischemic areas, and a significantly reduced loss in the primary infarct tissue. An autoradiographic analysis of brain coronal sections using 3H-ouabain supports the enzymatic data and GM1 effects. Reductions in 3H-ouabain binding in all cortical layers at 3 days after ischemia were visualized. GM1 treatment significantly reduced these 3H- ouabain binding losses. In summary, time-dependent quantitative changes in activity levels of ATPase isozymes (α+ and α) reflect the different degree of membrane damage that occurs in primary vs. peri-ischemic tissues (e.g., irreversible vs. reversible membrane damage), and that ischemia affects cell membranes of all neural elements in a largely similar fashion. GM1 ganglioside was found to reduce plasma membrane damage in all CNS cell types.

CT Medical Descriptors:
*brain ischemia: ET, etiology
*membrane damage
*membrane structure
animal model
animal tissue
article
autoradiography
brain cortex
cell membrane
cell protection
controlled study
enzyme activity
frontal lobe
male
nonhuman
occipital lobe
parietal lobe
priority journal
rat
temporal lobe
Drug Descriptors:
*adenosine triphosphatase (potassium sodium): EC, endogenous compound
*ganglioside gm1: PK, pharmacokinetics
*ganglioside gm1: PD, pharmacology

RN (ganglioside gm1) 37758-47-7

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reserved on STN DUPLICATE 17
ACCESSION NUMBER: 87128588 EMBASE
DOCUMENT NUMBER: 1987128588
TITLE: Effects of L-carnitine on phospholipids in the ischemic myocardium.
AUTHOR: Nagao B.; Kobayashi A.; Yamazaki N.
CORPORATE SOURCE: Third Department of Internal Medicine, Hamamatsu University School of Medicine, Hamamatsu 431-31, Japan
SOURCE: Japanese Heart Journal, (1987) Vol. 28, No. 2, pp. 243-251.
.
CODEN: JHEJAR
COUNTRY: Japan
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
LANGUAGE: English
ENTRY DATE: Entered STN: 11 Dec 1991
Last Updated on STN: 11 Dec 1991
ED Entered STN: 11 Dec 1991
Last Updated on STN: 11 Dec 1991
AB To evaluate to protective effects of L-carnitine on the **ischemic** myocardium, the effects of its **administration** on tissue levels of high energy phosphate and phospholipids were studied in ischemic dog hearts. Myocardial ischemia was induced by the ligation of the left anterior descending coronary artery for 40 min. In the experiment, L-carnitine (300 mg/kg) was administered intravenously prior to coronary artery ligation. Mitochondrial phospholipids were extracted from nonischemic and ischemic regions of the myocardium and subsequently analyzed. In ischemic myocardial tissues, levels of adenosine 5'-triphosphate (ATP) were reduced. The decrease was significantly elevated by L-carnitine pretreatment. The mitochondrial fractions obtained from ischemic myocardia had significantly lower levels of phospholipids than those obtained from nonischemic tissues. Moreover, the amounts of phosphatidylcholine, phosphatidylinositol and phosphatidylethanolamine were significantly decreased in ischemic myocardial tissues. L-carnitine-pretreatment prevented the reduction of these phospholipids. Lysophosphatidylethanolamine and **sphingomyelin** did not show statistically significant decreases. This may explain why the **administration** of carnitine has beneficial effects on **ischemic** myocardium.
CT Medical Descriptors:
*dog
*drug efficacy
*heart muscle ischemia
mitochondrion
priority journal
intravenous drug administration
nonhuman
heart
animal model
Drug Descriptors:
*carnitine
*phospholipid
adenosine triphosphate
RN (carnitine) 461-06-3, 541-15-1, 56-99-5; (adenosine triphosphate) 15237-44-2, 56-65-5, 987-65-5
CO Earth chemical

L161 ANSWER 82 OF 127 EMBASE

reserved on STN
ACCESSION NUMBER: 2000149800 EMBASE
TITLE: Damage-induced neuronal endopeptidase (DINE) is a unique metallopeptidase expressed in response to neuronal damage and activates superoxide scavengers.
AUTHOR: Kiryu-Seo S.; Sasaki M.; Yokohama H.; Nakagomi S.; Hirayama T.; Aoki S.; Wada K.; Kiyama H.
CORPORATE SOURCE: H. Kiyama, Department of Anatomy, Asahikawa Medical College, 2-1-1-1 Midorigaoka-Higashi, Asahikawa 078-8510, Japan. kiyama@asahikwa-med.ac.jp
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (11 Apr 2000) Vol. 97, No. 8, pp. 4345-4350. .
Refs: 40
ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 11 May 2000
Last Updated on STN: 11 May 2000
ED Entered STN: 11 May 2000
Last Updated on STN: 11 May 2000
AB We isolated a membrane-bound metallopeptidase, DINE (damage-induced neuronal endopeptidase), by differential display PCR using rat normal and axotomized hypoglossal nuclei. The most marked properties of DINE were neuron-specific expression and a striking response to axonal injury in both the central nervous system and peripheral nervous system. For instance, cranial and spinal nerve transection, **ischemia**, corpus callosum transection, and colchicine **treatment** increased DINE mRNA expression in the injured neurons, whereas kainate-induced hyperexcitation, immobilization, and osmotic stress failed to up-regulate DINE mRNA. Expression of DINE in COS cells partially inhibited C2-**ceramide**-induced apoptosis, probably because of the activation of antioxidant enzymes such as Cu/Zn-superoxide dismutase, Mn- superoxide dismutase, and glutathione peroxidase through the proteolytic activity of DINE. These data provide insight into the mechanism of how injured neurons protect themselves against neuronal death.
CT Medical Descriptors:
*gene expression
*nerve cell lesion
*gene activation
gene control
nerve transection
protein degradation
gene activity
neuroprotection
nerve cell necrosis
enzyme activation
nonhuman
male
rat
controlled study
animal tissue
animal cell
article
priority journal
Drug Descriptors:

*proteinase
*metalloproteinase
*superoxide
*scavenger
copper zinc superoxide dismutase
manganese superoxide dismutase
glutathione peroxidase
RN (proteinase) 9001-92-7; (metalloproteinase) 81669-70-7; (superoxide) 11062-77-4; (glutathione peroxidase) 9013-66-5

L161 ANSWER 83 OF 127 EMBASE
ACCESSION NUMBER: 2000193008 EMBASE
TITLE: Interrelationship between protein phosphatase-2A and cytoskeletal architecture during the endothelial cell response to soluble products produced by human head and neck cancer.
AUTHOR: Witt C.J.; Gabel S.P.; Meisinger J.; Werra G.; Liu S.W.; Young M.R.I.
CORPORATE SOURCE: Dr. M.R.I. Young, Research Services, Building 1, Hines VA Hospital, Hines, IL 60141, United States
SOURCE: Otolaryngology - Head and Neck Surgery, (2000) Vol. 122, No. 5, pp. 721-727. .
Refs: 23
ISSN: 0194-5998 CODEN: OTOLDL
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
011 Otorhinolaryngology
016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 22 Jun 2000
Last Updated on STN: 22 Jun 2000
ED Entered STN: 22 Jun 2000
Last Updated on STN: 22 Jun 2000
AB Tumor neovascularization is necessary for the progressive development of all solid tumors, including head and neck squamous cell carcinomas (HNSCCs). The angiogenic process includes increased endothelial cell motility. Our prior studies have shown the importance of protein phosphatase-2A (PP-2A) in restricting endothelial cell motility. Because motility is regulated by the polymerization/depolymerization of the cellular cytoskeleton, the present study defined the interrelationship between PP-2A and the cytoskeleton during endothelial cell responses to HNSCC-derived angiogenic factors. PP-2A was shown to colocalize with microtubules of unstimulated endothelial cells. However, exposure to HNSCC-derived products resulted in a more diffuse distribution of PP-2A staining and a loss of filamentous tubulin. The feasibility of pharmacologically **preventing** this cytoskeletal disorganization as a means of blocking tumor-induced **angiogenesis** was tested. This was accomplished by use of 1α,25-dihydroxyvitamin D3 [1,25 (OH)2D3) and all- trans-retinoic acid to indirectly stimulate PP-2A activity through their capacity to elevated intracellular levels of the second messenger **ceramide.** Pretreatment of endothelial cells with either 1,25(OH)2D3 or retinoic acid prevented the cytoskeletal disorganization that otherwise occurs in endothelial cells on exposure to HNSCC-derived products. These studies support the feasibility of using elevation of PP-2A to **prevent** the morphogenic component of the **angiogenic** process that is stimulated by HNSCC- derived factors.
CT Medical Descriptors:

*head and neck cancer: ET, etiology
solid tumor: ET, etiology
endothelium cell
cytoskeleton
microtubule
angiogenesis
human
human cell
article
Drug Descriptors:
*phosphoprotein phosphatase 2A
retinoic acid
calcitriol
RN (retinoic acid) 302-79-4; (calcitriol) 32222-06-3, 32511-63-0, 66772-14-3

L161 ANSWER 84 OF 127 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2000302020 EMBASE
TITLE: Local delivery of **ceramide** for **restenosis** : Is there a future for lipid **therapy**?.
AUTHOR: Kolodgie F.D.; Farb A.; Virmani R.
CORPORATE SOURCE: Dr. R. Virmani, Dept. of Cardiovascular Pathology, Armed Forces Institute of Pathology, 6825 16th St NW, Washington, DC 20306-6000, United States. virmani@afip.osd.mil
SOURCE: Circulation Research, (18 Aug 2000) Vol. 87, No. 4, pp. 264-267. .
Refs: 37
ISSN: 0009-7330 CODEN: CIRUAL
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 14 Sep 2000
Last Updated on STN: 14 Sep 2000
ED Entered STN: 14 Sep 2000
Last Updated on STN: 14 Sep 2000
AB How a structurally simple molecule like **ceramide** is able to **mediate** so many different, and sometimes paradoxical, physiological responses ranging from cell proliferation and differentiation to inhibition of cell growth and apoptosis is unknown. Moreover, crosstalk between **ceramide-induced** signal transduction cascades and other signaling pathways will add to the inherent difficulty in distinguishing the specific **effects** of **ceramide** in vascular biology. Although the study by Charles et al shows promise, this is the first step toward our understanding of the actions of **ceramide** on restenosis in vivo. Clearly, some of the vascular targets of **ceramide** could be clarified through studies using animals harboring **disrupted** genes of **sphingolipid** metabolism. More extensive research on the interaction of **ceramide** with specific cell types, especially in more complex models of restenosis using stents, is needed. More importantly, a clearer understanding of how vessels renarrow, particularly with stents, may help decipher the signaling pathways that promote **restenosis**; only then can the development of new **therapeutic** strategies be clinically effective.
CT Medical Descriptors:
*restenosis: DT, drug therapy
*coronary artery obstruction: DT, drug therapy

drug use
treatment outcome
transluminal coronary angioplasty
coronary artery blood flow
human
review
priority journal
Drug Descriptors:
***ceramide glucosyltransferase inhibitor: AD, drug administration**
***ceramide glucosyltransferase inhibitor: DT, drug therapy**

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ACCESSION NUMBER: 2000260492 EMBASE
TITLE: First clinical trial with etomoxir in patients with chronic congestive heart failure.
AUTHOR: Schmidt-Schweda S.; Holubarsch C.
CORPORATE SOURCE: Prof. C. Holubarsch, Medizinische Universitatsklinik, University of Freiburg, Department of Cardiology Angiology, Hugstetter Strasse 55, 79106 Freiburg, Germany. holubarsch@med1.ukl.uni-freiburg.de
SOURCE: Clinical Science, (2000) Vol. 99, No. 1, pp. 27-35. .
Refs: 67
ISSN: 0143-5221 CODEN: CSCIAE
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 10 Aug 2000
Last Updated on STN: 10 Aug 2000
ED Entered STN: 10 Aug 2000
Last Updated on STN: 10 Aug 2000

AB In the failing human myocardium, both impaired calcium homoeostasis and alterations in the levels of contractile proteins have been observed, which may be responsible for reduced contractility as well as diastolic dysfunction. In addition, levels of a key protein in calcium cycling, i.e. the sarcoplasmic reticulum Ca2+-ATPase, and of the α-myosin heavy chain have been shown to be enhanced by treatment with etomoxir, a carnitine **palmitoyltransferase** inhibitor, in normal and pressure-overloaded rat myocardium. We therefore studied, for the first time, the influence of long-term oral application of etomoxir on cardiac function in patients with chronic heart failure. A dose of 80 mg of etomoxir was given once daily to 10 patients suffering from heart failure (NYHA functional class II-III; mean age 55 ± 4 years; one patient with ischaemic heart disease and nine patients with dilated idiopathic cardiomyopathy; all male), in addition to standard therapy. The left ventricular ejection fraction was measured echocardiographically before and after a 3-month period of treatment. Central haemodynamics at rest and exercise (supine position bicycle) were defined by means of a pulmonary artery catheter and thermodilution. All 10 patients improved clinically; no patient had to stop taking the study medication because of side effects; and no patient died during the 3-month period. Maximum cardiac output during exercise increased from 9.72 ± 1.25 l/min before to 13.44 ± 1.50 l/min after **treatment** ($P < 0.01$); this increase was mainly due to an increased **stroke** volume [84 ± 7

ml before and 109 ± 9 ml after **treatment** (P < 0.01)].
Resting heart rate was slightly reduced (not statistically significant). During exercise, for any given heart rate, stroke volume was significantly enhanced (P < 0.05). The left ventricular ejection fraction increased significantly from 21.5 ± 2.6% to 27.0 ± 2.3% (P < 0.01). In acute studies, etomoxir showed neither a positive inotropic effect nor vasodilatory properties. Thus, although the results of this small pilot study are not placebo-controlled, all patients seem to have benefitted from etomoxir treatment. Etomoxir, which has no acute inotropic or vasodilatory properties and is thought to increase gene expression of the sarcoplasmic reticulum Ca2+-ATPase and the α-myosin heavy chain, improved clinical status, central haemodynamics at rest and during exercise, and left ventricular ejection fraction.

CT Medical Descriptors:
*congestive heart failure: DT, drug therapy
artery catheter
bicycle ergometer
echocardiography
exercise
gene expression
heart dilatation: DT, drug therapy
heart function
heart hemodynamics
heart left ventricle ejection fraction
heart output
heart rate
heart stroke volume
inotropism
ischemic heart disease: DT, drug therapy
sarcoplasmic reticulum
side effect: SI, side effect
vasodilatation
human
clinical article
human tissue
clinical trial
male
aged
adult
article
priority journal
Drug Descriptors:
*etomoxir: AE, adverse drug reaction
*etomoxir: CT, clinical trial
*etomoxir: DT, drug therapy
*etomoxir: PO, oral drug administration
adenosine triphosphatase (calcium): EC, endogenous compound
beta adrenergic receptor blocking agent: DT, drug therapy
digoxin: CB, drug combination
digoxin: DT, drug therapy
dipeptidyl carboxypeptidase inhibitor: CB, drug combination
dipeptidyl carboxypeptidase inhibitor: DT, drug therapy
diuretic agent: CB, drug combination
diuretic agent: DT, drug therapy
myosin heavy chain: EC, endogenous compound

RN (etomoxir) 82258-36-4; (digoxin) 20830-75-5, 57285-89-9

L161 ANSWER 86 OF 127 EMBASE

ACCESSION NUMBER: 2000063165 EMBASE

TITLE: Regulation of carbohydrate metabolism in ischemia and reperfusion.
AUTHOR: Lopaschuk G.
CORPORATE SOURCE: Dr. G. Lopaschuk, Cardiovascular Research Group, University of Alberta, 423 Heritage Medical Research Center, Edmonton, Alta. T6G-2S2, Canada. gary.lopaschuk@ualberta.ca
SOURCE: American Heart Journal, (2000) Vol. 139, No. 2 III, pp. S115-S119. .
Refs: 28
ISSN: 0002-8703 CODEN: AHJOA2
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 2 Mar 2000
Last Updated on STN: 2 Mar 2000
ED Entered STN: 2 Mar 2000
Last Updated on STN: 2 Mar 2000
AB **Administration** of L-carnitine reduces **ischemic myocardial injury** in a number of experimental model systems and may improve the clinical outcomes of patients with acute myocardial infarction. The efficacy of carnitine in this setting is probably not attributable to an increase in fatty acid oxidation, which can be detrimental to myocardial recovery during reperfusion. Instead, recent research suggests that carnitine is also crucial in the regulation of carbohydrate metabolism in addition to its role in the oxidation of fatty acids. In isolated rat hearts, administration of carnitine increases the oxidation of glucose while decreasing the oxidation of palmitate. This increase in carbohydrate metabolism is accompanied by a significant improvement of contractile function during reperfusion of ischemic hearts. The beneficial effects of carnitine seen in patients after an acute MI may be attributable to an improvement in myocardial energy metabolism. Controlled clinical trials will be useful in confirming the results from these experimental studies.
CT Medical Descriptors:
*carbohydrate metabolism
*heart muscle ischemia: DT, drug therapy
*heart muscle reperfusion
heart muscle metabolism
fatty acid oxidation
glucose oxidation
heart muscle contractility
acute heart infarction: DT, drug therapy
drug effect
fatty acid transport
treatment outcome
human
nonhuman
conference paper
priority journal
Drug Descriptors:
*carbohydrate
*carnitine: DT, drug therapy
*carnitine: PD, pharmacology
glucose: EC, endogenous compound
fatty acid: EC, endogenous compound
palmitic acid: EC, endogenous compound

acetyl coenzyme A: EC, endogenous compound
adenosine triphosphate: EC, endogenous compound
carnitine palmitoyltransferase: EC, endogenous compound
malonyl coenzyme A: EC, endogenous compound

RN (carnitine) 461-06-3, 541-15-1, 56-99-5; (glucose) 50-99-7, 84778-64-3; (palmitic acid) 57-10-3; (acetyl coenzyme A) 72-89-9; (adenosine triphosphate) 15237-44-2, 56-65-5, 987-65-5; (carnitine **palmitoyltransferase**) 9068-41-1; (malonyl coenzyme A) 524-14-1

L161 ANSWER 87 OF 127 EMBASE

ACCESSION NUMBER: 1998381808 EMBASE
TITLE: Signal transduction of stress via ceramide.
AUTHOR: Mathlas S.; Pena L.A.; Kolesnick R.N.
CORPORATE SOURCE: R.N. Kolesnick, Laboratory of Signal Transduction, Memorial Sloan-Kettering Cancer Ctr., 1275 York Ave., New York, NY 10021, United States. r-kolesnick@ski.mskcc.org
SOURCE: Biochemical Journal, (1 Nov 1998) Vol. 335, No. 3, pp. 465-480. .
Refs: 303
ISSN: 0264-6021 CODEN: BIJOAK
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 30 Nov 1998
Last Updated on STN: 30 Nov 1998

ED Entered STN: 30 Nov 1998
Last Updated on STN: 30 Nov 1998

AB The **sphingomyelin** (SM) pathway is a ubiquitous, evolutionarily conserved signalling system analogous to conventional systems such as the cAMP and phosphoinositide pathways. Ceramide, which serves as second messenger in this pathway, is generated from SM by the action of a neutral or acidic **SMase**, or by de novo synthesis co-ordinated through the enzyme ceramide synthase. A number of direct targets for ceramide action have now been identified, including ceramide-activated protein kinase, ceramide-activated protein phosphatase and protein kinase Cζ which couple the SM pathway to well defined intracellular signalling cascades. The SM pathway induces differentiation, proliferation or growth arrest, depending on the cell type. Very often, however, the outcome of signalling through this pathway is apoptosis. Mammalian systems respond to diverse stresses with ceramide generation, and recent studies show that yeast manifest a form of this response. Thus ceramide signalling is an older stress response system than the caspase/apoptotic death pathway, and hence these two pathways must have become linked later in evolution. Signalling of the stress response through ceramide appears to play a role in the development of human diseases, including **ischaemia** /reperfusion injury, insulin resistance and diabetes, atherogenesis, septic shock and ovarian failure. Further, **ceramide** signalling **mediates** the therapeutic **effects** of chemotherapy and radiation in some cells. An understanding of the mechanisms by which **ceramide regulates** physiological and pathological events in specific cells may provide new targets for pharmacological intervention.

CT Medical Descriptors:
*signal transduction
*stress
genetic conservation

cell differentiation
cell proliferation
apoptosis
mammal
yeast
ischemia
reperfusion injury
insulin resistance
diabetes mellitus
atherogenesis
septic shock
ovary insufficiency
physiology
human
nonhuman
review
priority journal
Drug Descriptors:
*ceramide: EC, endogenous compound
sphingomyelin: EC, endogenous compound
cyclic amp: EC, endogenous compound
phosphatidylinositide: EC, endogenous compound
protein kinase: EC, endogenous compound
cysteine proteinase: EC, endogenous compound
RN (**sphingomyelin**) 85187-10-6; (cyclic amp) 60-92-4; (protein kinase) 9026-43-1; (cysteine proteinase) 37353-41-6

L161 ANSWER 88 OF 127 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1998265605 EMBASE
TITLE: A synthetic **ceramide** analog (L-PDMP) up-regulates neuronal function.
AUTHOR: Inokuchi J.-I.; Mizutani A.; Jimbo M.; Usuki S.; Yamagishi K.; Mochizuki H.; Muramoto K.; Kobayashi K.; Kuroda Y.; Iwasaki K.; Ohgami Y.; Fujiwara M.
CORPORATE SOURCE: J.-I. Inokuchi, Dept Biomembrane Biofunctional Chem, Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan
SOURCE: Annals of the New York Academy of Sciences, (1998) Vol. 845, pp. 219-224. .
Refs: 7
ISSN: 0077-8923 CODEN: ANYAA
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 008 Neurology and Neurosurgery
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 27 Aug 1998
Last Updated on STN: 27 Aug 1998
ED Entered STN: 27 Aug 1998
Last Updated on STN: 27 Aug 1998
AB To address the role of brain gangliosides in synaptic activity, the **ceramide** analogs, D-threo-1-phenyl-2-decanoylamino-3-morpholino (D-PDMP) and its enantiomer, L-PDMP, were used to inhibit and stimulate ganglioside biosynthesis in cultured cortical neurons. Prolonged treatment with both PDMP isomers exhibited opposite effects on functional synapse formation measured by spontaneous synchronized oscillatory activity of intracellular Ca2+ between the neurons: suppression by D-PDMP and facilitation by L-PDMP, Up-regulation of synaptic activity by L-PDMP

could be correlated with the slow but robust activation of p42 mitogen-activated protein kinase. **Treatment** with L-PDMP after transient forebrain **ischemia** in rats ameliorated the deficit of a well-learned spatial memory by an 8-arm maze task, suggesting a new potential therapeutic approach for neurodegenerative disorders.

CT Medical Descriptors:
*nerve function
synapse
enantiomer
nerve cell culture
brain cell
brain cortex
synaptogenesis
calcium cell level
facilitation
forebrain
brain ischemia
spatial memory
maze test
nerve degeneration
nonhuman
rat
controlled study
animal cell
embryo
conference paper
Drug Descriptors:
***ceramide**
*2 decanoylamino 3 morpholino 1 phenyl 1 propanol
calcium ion: EC, endogenous compound
mitogen activated protein kinase: EC, endogenous compound

RN (2 decanoylamino 3 morpholino 1 phenyl 1 propanol) 109836-82-0, 73257-80-4; (calcium ion) 14127-61-8; (mitogen activated protein kinase) 142243-02-5

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ACCESSION NUMBER: 97312507 EMBASE
DOCUMENT NUMBER: 1997312507
TITLE: Up-regulation of ganglioside biosynthesis, functional synapse formation, and memory retention by a synthetic **ceramide** analog (L-PDMP).
AUTHOR: Inokuchi J.I.; Mizutani A.; Jimbo M.; Usuki S.; Yamagishi K.; Mochizuki H.; Muramoto K.; Kobayashi K.; Kuroda Y.; Iwasaki K.; Ohgami Y.; Fujiwara M.
CORPORATE SOURCE: J.I. Inokuchi, Tokyo Research Institute, Seikagaku Corporation, 1253 Tateno 3-chome, Higashiyamato, Tokyo 207, Japan. inokuchijin@jsn.justnet.or.jp
SOURCE: Biochemical and Biophysical Research Communications, (1997) Vol. 237, No. 3, pp. 595-600. .
Refs: 38
ISSN: 0006-291X CODEN: BBRCA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 30 Oct 1997
Last Updated on STN: 30 Oct 1997
ED Entered STN: 30 Oct 1997
Last Updated on STN: 30 Oct 1997
AB To address the role of brain gangliosides in synaptic activity, the **ceramide** analogs, D-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol (D-PDMP) and its enanatiomer, L-PDMP, were used to inhibit and stimulate ganglioside biosynthesis in cultured cortical neurons. Prolonged treatment with both PDMP isomers exibited opposite effects on functional synapse formation measured by spontaneous synchronized oscillatory activity of intracellular Ca2+ between the neurons: suppression by D-PDMP and facilitation by L-PDMP. Up-regulation of synaptic activity by L-PDMP could be correlated with the slow but robust stimulation of ganglioside biosynthesis through activating GM3, GD3 and GQ1b synthases. In a similar time couurse, the activity of p42 mitogen-activated protein kinase was also enhanced by L-PDMP. To evaluate the efficacy of this drug in long-term memory, rats were trained for 2 weeks using an 8-arm radial maze task, and theta forebrain **ischemia** was induced by 4-vessel occlusion, **Treatment** with L-PDMP starting 24 hours after the transient **ischemia** ameliorated the deficit of a well-learned spatial memory, demonstrating the potential therapeutic intervention of the **ceramide** analog for neurodegenerative disorders.
CT Medical Descriptors:
*lipogenesis
*memory consolidation
*synaptogenesis
animal experiment
animal tissue
article
brain ischemia
controlled study
enantiomer
enzyme activation
enzyme activity
intraperitoneal drug administration
long term memory
male
maze test
metabolic regulation
nerve cell culture
nonhuman
priority journal
rat
spatial memory
synapse
Drug Descriptors:
***ceramide derivative: AN, drug analysis**
*ganglioside: EC, endogenous compound
*neuroprotective agent: AN, drug analysis
2 decanoylamino 3 morpholino 1 phenyl 1 propanol
ganglioside gd3: EC, endogenous compound
ganglioside gm3: EC, endogenous compound
mitogen activated protein kinase: EC, endogenous compound
synthetase: EC, endogenous compound
RN (2 decanoylamino 3 morpholino 1 phenyl 1 propanol) 109836-82-0, 73257-80-4; (ganglioside gd3) 62010-37-1; (ganglioside gm3) 54827-14-4; (mitogen activated protein kinase) 142243-02-5; (synthetase) 9031-56-5, 9031-57-6

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ACCESSION NUMBER: 97293469 EMBASE
DOCUMENT NUMBER: 1997293469
TITLE: Pulmonary surfactant composition early in development of acute lung **injury** after **cardiopulmonary** bypass: Prophylactic use of surfactant **therapy.**
AUTHOR: Haslam P.L.; Baker C.S.; Hughes D.A.; Macnaughton P.D.; Moat N.E.; Dewar A.; Aggarwal A.; Evans T.W.
CORPORATE SOURCE: Dr. P.L. Haslam, Cell Biology Unit, National Heart and Lung Institute, Imperial College, Dovehouse Street, London SW3 6LY, United Kingdom
SOURCE: International Journal of Experimental Pathology, (1997) Vol. 78, No. 4, pp. 277-289. .
Refs: 42
ISSN: 0959-9673 CODEN: IJEPEI
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Oct 1997
Last Updated on STN: 16 Oct 1997

ED Entered STN: 16 Oct 1997
Last Updated on STN: 16 Oct 1997

AB Cardiopulmonary bypass surgery (CPB) causes lung injury and at least 2% of adult patients and more children develop the most severe form acute respiratory distress syndrome (ARDS). Pulmonary surfactant deficiency contributes to the pathogenesis of ARDS. It has been proposed that surfactant therapy immediately after CPB might arrest progression to ARDS. However, many patients develop only mild lung injury after CPB. Thus early markers are needed to identify those patients at highest risk to guide selection for treatment. The aim of this study was to determine whether changes in surfactant phospholipids occur, and reflect severity of lung injury within the first few hours after bypass. Because of the relatively low incidence of ARDS in adult patients, this study was conducted using young pigs highly susceptible to bypass-induced lung injury. Eight pigs were given 2 hours bypass. Six controls underwent 'sham' bypass. At 3 h after bypass pulmonary vascular endothelial permeability was assessed by transcapillary leakage of radiolabelled transferrin. A 4 hour broncho-alveolar lavage (BAL) was used to assess intra-alveolar levels of surfactant, inflammatory cells and oedema protein. Bypass caused falls in arterial oxygenation and lung compliance ($P< 0.01$), but at this early stage in progression of lung injury BAL surfactant phospholipid and albumin levels were within the control range indicating that the alveolar epithelium had not yet suffered major damage. The main abnormalities were increases in vascular endothelial permeability ($P<0.01$), BAL neutrophils ($P<0.01$), total protein and **sphingomyelin** (SM) ($P<0.05$). Lung histology showed that the main damage was interstitial oedema located around the bronchioles and their associated vessels. A single instilled dose of surfactant phospholipids in 5 animals caused excess in vivo supplementation and did not reduce the early pathophysiologic changes. Our findings suggest that surfactant phospholipid deficiency does not make a major contribution in the initial stages of lung injury after CPB, and that excessive phospholipid supplementation at this stage can be deleterious.

CT Medical Descriptors:
*cardiopulmonary bypass

*lung injury: PC, prevention
*lung injury: DT, drug therapy
acute disease
animal experiment
animal model
animal tissue
arterial oxygen saturation
article
capillary permeability
controlled study
lung lavage
male
nonhuman
priority journal
respiratory distress syndrome: PC, prevention
respiratory distress syndrome: DT, drug therapy
swine
Drug Descriptors:
*albumin: EC, endogenous compound
*lung surfactant: DT, drug therapy
*phosphatidylcholine: EC, endogenous compound
*phospholipid: EC, endogenous compound
***sphingomyelin: EC, endogenous compound**
*transferrin
artificial lung expanding compound
protein: EC, endogenous compound
unclassified drug
RN (lung surfactant) 99732-49-7; (phosphatidylcholine) 55128-59-1, 8002-43-5; (**sphingomyelin**) 85187-10-6; (transferrin) 82030-93-1; (protein) 67254-75-5
CN (1) Artificial lung expanding compound
CO (1) Britannia (United Kingdom)

L161 ANSWER 91 OF 127 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 97063671 EMBASE
DOCUMENT NUMBER: 1997063671
TITLE: Cellular signaling roles of TGFβ, TNFα and βAPP in brain injury responses and Alzheimer's disease.
AUTHOR: Mattson M.P.; Barger S.W.; Furukawa K.; Bruce A.J.; Wyss-Coray T.; Mark R.J.; Mucke L.
CORPORATE SOURCE: M.P. Mattson, Sanders-Brown Research Ctr. on Aging, University of Kentucky, Lexington, KY 40536-0230, United States. mmattson@aging.coa.uky.edu
SOURCE: Brain Research Reviews, (1997) Vol. 23, No. 1-2, pp. 47-61.
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Refs: 119
ISSN: 0165-0173 CODEN: BRERD2
PUBLISHER IDENT.: S 0165-0173(96)00014-8
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 4 Apr 1997
Last Updated on STN: 4 Apr 1997
ED Entered STN: 4 Apr 1997
Last Updated on STN: 4 Apr 1997

AB β-Amyloid precursor protein (βAPP), transforming growth factor β (TGFβ), and tumor necrosis factor-α (TNFα) are remarkably pleiotropic neural cytokines/neurotrophic factors that orchestrate intricate injury-related cellular and molecular interactions. The links between these three factors include: their responses to injury; their interactive effects on astrocytes, microglia and neurons; their ability to induce cytoprotective responses in neurons; and their association with cytopathological alterations in Alzheimer's disease. Astrocytes and microglia each produce and respond to TGFβ and TNFα in characteristic ways when the brain is injured. TGFβ, TNFα and secreted forms of βAPP (sAPP) can protect neurons against excitotoxic, metabolic and oxidative insults and may thereby serve neuroprotective roles. On the other hand, under certain conditions TNFα and the fibrillogenic amyloid β-peptide (Aβ) derivative of βAPP can promote damage of neuronal and glial cells, and may play roles in neurodegenerative disorders. Studies of genetically manipulated mice in which TGFβ, TNFα or βAPP ligand or receptor levels are altered suggest important roles for each factor in cellular responses to brain injury and indicate that mediators of neural injury responses also have the potential to enhance amyloidogenesis and/or to interfere with neuroregeneration if expressed at abnormal levels or modified by strategic point mutations. Recent studies have elucidated signal transduction pathways of TGFβ (serine/threonine kinase cascades), TNFα (p55 receptor linked to a **sphingomyelin-ceramide**-NFκB pathway), and secreted forms of βAPP (sAPP; receptor guanylate cyclase-cGMP-cGMP-dependent kinase-K+ channel activation). Knowledge of these signaling pathways is revealing novel molecular targets on which to focus neuroprotective **therapeutic** strategies in disorders ranging from **stroke** to Alzheimer's disease.

CT Medical Descriptors:
*alzheimer disease: ET, etiology
*astrocyte
*brain injury: ET, etiology
*microglia
*signal transduction
animal cell
animal tissue
human
human tissue
inflammation
nerve cell excitability
nonhuman
priority journal
review
Drug Descriptors:
*amyloid precursor protein: EC, endogenous compound
*cytokine: EC, endogenous compound
*reactive oxygen metabolite: EC, endogenous compound
*transforming growth factor beta: EC, endogenous compound
*tumor necrosis factor: EC, endogenous compound
neuroprotective agent

L161 ANSWER 92 OF 127 EMBASE

ACCESSION NUMBER: 97090363 EMBASE
DOCUMENT NUMBER: 1997090363
TITLE: Perhexiline improves symptomatic status in elderly patients with severe aortic stenosis.
AUTHOR: Unger S.A.; Robinson M.A.; Horowitz J.D.

CORPORATE SOURCE: Prof. J.D. Horowitz, Cardiology Unit, Queen Elizabeth Hospital, 28 Woodville Road, Woodville South, SA 5011, Australia
SOURCE: Australian and New Zealand Journal of Medicine, (1997) Vol. 27, No. 1, pp. 24-28. .
Refs: 13
ISSN: 0004-8291 CODEN: ANZJB8
COUNTRY: Australia
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 7 May 1997
Last Updated on STN: 7 May 1997
ED Entered STN: 7 May 1997
Last Updated on STN: 7 May 1997

AB Background: The prognosis of severe symptomatic aortic stenosis is poor without aortic valve replacement, with no previous reports of beneficial effects of any medical treatment on either symptoms or outcome. However, this condition is increasingly a disease of the elderly and cardiothoracic surgery is associated with significant mortality and morbidity in this group. Aims: We postulated that perhexiline, a novel anti-ischaemic agent with an oxygen-sparing metabolic effect in the myocardium (via inhibition of carnitine **palmitoyltransferase**-1) and no adverse haemodynamic effects, may improve symptomatic status in elderly patients with severe aortic stenosis. We report here our initial experience with perhexiline treatment in such patients. Methods: Elderly patients with-symptomatic severe aortic **stenosis**, who were deemed unsuitable for aortic valve replacement, were **treated** with perhexiline, the drug dosage titrated according to steady state plasma perhexiline concentrations. NYHA functional class was determined prior to and three months following commencement of perhexiline, and changes were analysed using McNemar's test. Results: Fifteen patients, age range 73-87, were followed for up to 30 months (median 18 months). Symptomatic status improved in 13 of the 15 patients over the first three months of perhexiline therapy ($p<0.01$), five patients becoming asymptomatic. Twelve month actuarial survival was 80% (95% CI=57, 100). Perhexiline was well tolerated with no withdrawals due to toxicity or deteriorating clinical status. Conclusion: Therapy with perhexiline was associated with a marked improvement in clinical status in this group of elderly patients with severe aortic stenosis.

CT Medical Descriptors:
*aorta stenosis
aged
article
clinical article
clinical trial
drug efficacy
drug tolerability
female
follow up
human
male
nausea
prognosis
vertigo

Drug Descriptors:
*perhexiline: DT, drug therapy
*perhexiline: AE, adverse drug reaction
*perhexiline: CT, clinical trial
RN (perhexiline) 6621-47-2

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ACCESSION NUMBER: 97000638 EMBASE
DOCUMENT NUMBER: 1997000638
TITLE: Long-chain triglycerides improve recovery from myocardial stunning in conscious dogs.
AUTHOR: Van De Velde M.; Wouters P.F.; Rolf N.; Van Aken H.; Flameng W.; Vandermeersch E.
CORPORATE SOURCE: P.F. Wouters, Department of Anaesthesiology, University Hospitals Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium
SOURCE: Cardiovascular Research, (1996) Vol. 32, No. 6, pp. 1008-1015. .
ISSN: 0008-6363 CODEN: CVREAU
PUBLISHER IDENT.: S 0008-6363(96)00165-4
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 12 Feb 1997
Last Updated on STN: 12 Feb 1997
ED Entered STN: 12 Feb 1997
Last Updated on STN: 12 Feb 1997

AB Objectives: Free fatty acid (FFA) oxidation is depressed in the postischaemic stunned myocardium and recovers in parallel with the normalization of contractile performance. Assuming a causal role for this metabolic disturbance in the pathogenesis of stunning, we questioned whether exogenous **administration** of high dose triglycerides during **reperfusion** of postischaemic myocardium, could improve its functional recovery. Methods: Thirteen dogs were chronically instrumented to measure global and regional haemodynamics and to produce a 10 min episode of regional myocardial ischaemia. In 7 dogs, Intralipid® 20% was **administered** i.v. during the **reperfusion** phase. Contractile recovery of stunned myocardium was compared with control saline treatments. The series were repeated in another 6 animals, but oxfenicine (CPT I inhibitor) preceded Intralipid® during reperfusion. Results: Contractile recovery of stunned myocardium was faster and more extensive when Intralipid® was **administered** during **reperfusion** than with saline **treatment** (wall thickening fraction 86 ± 6% of preischaemic controls versus 52 ± 11% at 90 min post-reperfusion; $P < 0.05$). Oxfenicine pretreatment completely abolished this beneficial effect. Conclusions: Exogenous **administration** of triglycerides during **reperfusion** of postischaemic myocardium improves functional recovery from stunning. This beneficial effect most likely operates through enhanced FFA availability and/or oxidation since it could be abolished by selective inhibition of the carnitine **palmitoyl transferase** I enzyme.

CT Medical Descriptors:
*heart muscle ischemia
*stunned heart muscle

animal experiment
article
controlled study
intravenous drug administration
nonhuman
priority journal
Drug Descriptors:
*fatty acid
*intralipid: PD, pharmacology
*long chain triacylglycerol: PD, pharmacology
oxfenicine
RN (intralipid) 68890-65-3; (oxfenicine) 32462-30-9, 938-97-6
CN (1) Intralipid
CO (1) Kabi (Sweden)

L161 ANSWER 94 OF 127 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 96175395 EMBASE
DOCUMENT NUMBER: 1996175395
TITLE: Pyruvate dehydrogenase activity and malonyl CoA levels in normal and ischemic swine myocardium: Effects of dichloroacetate.
AUTHOR: Stanley W.C.; Hernandez L.A.; Spires D.; Bringas J.; Wallace S.; McCormack J.G.
CORPORATE SOURCE: CV Therapeutics, 3172 Porter Drive,Palo Alto, CA 94304, United States
SOURCE: Journal of Molecular and Cellular Cardiology, (1996) Vol. 28, No. 5, pp. 905-914. .
ISSN: 0022-2828 CODEN: JMCDAY
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 8 Jul 1996
Last Updated on STN: 8 Jul 1996
ED Entered STN: 8 Jul 1996
Last Updated on STN: 8 Jul 1996
AB The purposes of this study were to: (1) assess myocardial pyruvate dehydrogenase (PDH) activity and substrate exchange under well-perfused and ischemic conditions; (2) determine the metabolic effects of an intra-coronary infusion of the PDH activator, dichloroacetate (DCA); and (3) measure the effects of ischemia and DCA on malonyl CoA levels. Experiments were performed in anesthetised open-chest swine under non-ischemic conditions, followed by 40 min with a 60% reduction in left anterior descending coronary artery (LAD) blood now. Myocardial needle biopsies for measurement of PDH activity were taken after an intracoronary infusion of either saline or DCA (1 mM in LAD blood) under aerobic conditions, and after 37 min of ischemia. Pyruvate dehydrogenase activity was measured with and without maximal activation by swine PDH phosphatase. Malonyl CoA and acetyl CoA were measured after 40 min of LAD **ischemia** in myocardium from the **ischemic** DCA- or saline-**treated** LAD bed, and the non-**ischemic** untreated left circumflex coronary artery (CFX) perfusion bed. Net glucose, lactate and free fatty acid (FFA) uptakes were measured across the LAD perfusion bed throughout the study. Dichloroacetate treatment increased the amount of active dephosphorylated PDH to 88% of the total activity under aerobic conditions, compared to 55% with saline ($P < 0.01$), Ischemia did not significantly change PDH activation state in either group, Acetyl CoA and

malonyl CoA contents were significantly elevated in **ischemic** DCA-**treated** myocardium compared to saline-**treated** **ischemic** myocardium. Dichloroacetate treatment significantly lowered rates of myocardial FFA uptake under both aerobic and ischemic conditions, but did not effect glucose uptake or lactate exchange, Free fatty acid uptake was negatively correlated to malonyl CoA levels (r= -0.68) during ischemia. It is proposed that the inhibition of FFA uptake observed with DCA in ischemic myocardium is due to malonyl CoA inhibition of carnitine **palmitoyl transferase** I.

CT Medical Descriptors:
*enzyme activity
*heart muscle ischemia: ET, etiology
animal experiment
animal model
animal tissue
article
controlled study
coronary artery circumflex branch
enzyme inhibition
enzyme substrate
heart mitochondrion
heart muscle metabolism
left anterior descending coronary artery
male
needle biopsy
nonhuman
priority journal
swine
tissue level
Drug Descriptors:
*dichloroacetic acid
*malonyl coenzyme a: EC, endogenous compound
*pyruvate dehydrogenase: EC, endogenous compound
acetyl coenzyme a: EC, endogenous compound
carnitine palmitoyltransferase: EC, endogenous compound
fatty acid: EC, endogenous compound
glucose: EC, endogenous compound
lactic acid: EC, endogenous compound
pyruvate dehydrogenase phosphatase

RN (dichloroacetic acid) 13425-80-4, 2156-56-1, 79-43-6; (malonyl coenzyme a) 524-14-1; (pyruvate dehydrogenase) 9014-20-4; (acetyl coenzyme a) 72-89-9; (carnitine **palmitoyltransferase**) 9068-41-1; (glucose) 50-99-7, 84778-64-3; (lactic acid) 113-21-3, 50-21-5; (pyruvate dehydrogenase phosphatase) 9073-70-5

L161 ANSWER 95 OF 127 EMBASE

ACCESSION NUMBER: 96070022 EMBASE
DOCUMENT NUMBER: 1996070022
TITLE: Role of gangliosides in tumour progression: A molecular target for cancer therapy?.
AUTHOR: Fish R.G.
CORPORATE SOURCE: Cancer Biology/Pharmacology Unit, Velindre NHS Trust Hospital,Cardiff CF4 7XL, United Kingdom
SOURCE: Medical Hypotheses, (1996) Vol. 46, No. 2, pp. 140-144. .
ISSN: 0306-9877 CODEN: MEHYDY
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
037 Drug Literature Index

LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 25 Mar 1996
Last Updated on STN: 25 Mar 1996
ED Entered STN: 25 Mar 1996
Last Updated on STN: 25 Mar 1996
AB In a number of patients with tumours of either neuroectodermal or epithelial origin, polysialylated gangliosides (e.g. GD3) are over-expressed. The mechanism of ganglioside over-expression may be different for the two classes of tumour and could represent distinct secondary genetic mutations or epigenetic changes affecting the enzymes (transferases and/or hydrolases) controlling the metabolic interconversions of these gangliosides. Tumour cells of neuroectodermal origin (e.g. melanomas and brain tumours) are known to produce and shed polysialylated gangliosides, whereas paracrine signal(s) from tumour cells of epithelial origin (e.g. carcinomas of cervix, lung, prostate, breast, head and neck, colon and ovary) may stimulate over-expression and shedding from tumour infiltrating mesenchymal cells (e.g. macrophages and/or fibroblasts). This cellular membrane overexpression and shedding of acidic **glycosphingolipids** into the interstitial spaces and blood of cancer patients may play a central role in increased tumour cell growth, lack of immune cell recognition and **neovascularization** and could represent a molecular target for cancer **therapy.**
CT Medical Descriptors:
*cancer therapy
*tumor: ET, etiology
*tumor: DT, drug therapy
*tumor growth
article
gene expression
human
hypothesis
priority journal
Drug Descriptors:
*ganglioside: EC, endogenous compound
*ganglioside antibody: DT, drug therapy
*monoclonal antibody: DT, drug therapy

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ACCESSION NUMBER: 95185976 EMBASE
DOCUMENT NUMBER: 1995185976
TITLE: Selected metabolic alterations in the ischemic heart and their contributions to arrhythmogenesis.
AUTHOR: Corr P.B.; Yamada K.A.
CORPORATE SOURCE: Searle Research and Development, c/o Monsanto Company, 700 Chesterfield Village Parkway No.,Chesterfield, MO 63198, United States
SOURCE: Herz, (1995) Vol. 20, No. 3, pp. 156-168. .
ISSN: 0340-9937 CODEN: HERZDW
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English; German
ENTRY DATE: Entered STN: 9 Aug 1995
Last Updated on STN: 9 Aug 1995

ED Entered STN: 9 Aug 1995
Last Updated on STN: 9 Aug 1995

AB Myocardial ischemia in vivo is associated with dramatic electrophysiologic alterations which occur within minutes of cessation of coronary flow and are rapidly reversible with reperfusion. This suggests that subtle and reversible biochemical and/or ionic alterations within or near the sarcolemma may contribute to the electrophysiologic derangements. Our studies have concentrated on 2 amphipathic metabolites long-chain acylcarnitines and lysophosphatidylcholine (LPC) which have been shown to increase rapidly in ischemic tissue in vivo and to elicit electrophysiologic derangements in normoxic tissue in vitro. Incorporation of these amphiphiles into the sarcolemma at concentrations of 1 to 2 mol% elicits profound electrophysiologic derangements analogous to those observed in ischemic myocardium in vivo. LPC is produced in endothelial cells and myocytes in response to thrombin. Thus, activation of the coagulation system during ischemia may result in extracellular production and accumulation of LPC. The pathophysiological effects of the accumulation of both amphiphiles are thought to be mediated by alterations in the biophysical properties of the sarcolemmal membrane, although there is a possibility of a direct effect on ion channels. Inhibition of carnitine acyltransfcrase I in the **ischemic** cat heart was found to **prevent** the increase in both long-chain acylcarnitines and LPC and to significantly reduce the incidence of malignant arrhythmias including ventricular tachycardia and fibrillation. This review focuses on the influence of these amphiphiles on cardiac ionic currents observed during early ischemia and presents data supporting the concept that accumulation of these amphiphiles within the sarcolemma contributes to changes in ionic conductances leading to electrophysiological derangements. The contribution and the accumulation of these amphiphiles to alterations in intracellular Ca2+ as related to changes in Na/K-ATPase activity and intracellular Na+ are examined. Other alterations occur during early myocardial ischemia in addition to the events reviewed here; however the results of multiple studies over the past 2 decades indicate that accumulation of these amphiphiles contributes importantly to arrhythmogenesis and that development of specific inhibitors of carnitine acyltransferase I or phospholipase A2 may be a promising **therapeutic** strategy to attenuate the incidence of lethal arrhythmias associated with **ischemic** heart discase in man.

CT Medical Descriptors:
*heart arrhythmia: ET, etiology
*heart arrhythmia: DT, drug therapy
*heart muscle ischemia: DT, drug therapy
arrhythmogenesis
enzyme activity
human
metabolism
review
Drug Descriptors:
*acylcarnitine: PD, pharmacology
*acylcarnitine: EC, endogenous compound
*enzyme inhibitor: DT, drug therapy
*enzyme inhibitor: DV, drug development
*lysophosphatidylcholine: PD, pharmacology
*lysophosphatidylcholine: EC, endogenous compound
*palmitoylcarnitine: PD, pharmacology
*palmitoylcarnitine: DT, drug therapy
carnitine palmitoyltransferase inhibitor: DT, drug therapy
carnitine palmitoyltransferase inhibitor: DV, drug development
phospholipase a2 inhibitor: DT, drug therapy
phospholipase a2 inhibitor: DV, drug development

unclassified drug
RN (lysophosphatidylcholine) 93794-93-5; (palmitoylcarnitine) 1935-18-8, 2364-67-2

L161 ANSWER 97 OF 127 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 96006208 EMBASE
DOCUMENT NUMBER: 1996006208
TITLE: Rebamipide ameliorates hepatic dysfunction induced by ischemia/reperfusion in rats.
AUTHOR: Lee S.-M.; Kim K.H.
CORPORATE SOURCE: Department of Pharmacology, Yonsei Univ. College of Medicine,Seoul 120-752, Korea, Republic of
SOURCE: European Journal of Pharmacology, (1995) Vol. 294, No. 1, pp. 41-46. .
ISSN: 0014-2999 CODEN: EJPHAZ
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry
048 Gastroenterology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 30 Jan 1996
Last Updated on STN: 30 Jan 1996
ED Entered STN: 30 Jan 1996
Last Updated on STN: 30 Jan 1996
AB The relationship between lipid peroxidation and alterations in hepatic secretory function and microsomal function during hepatic ischemia/reperfusion was studied. Rats pretreated with free radical scavengers were subjected to 60 min of hepatic ischemia and to 1 and 5 h of reperfusion thereafter. Serum aminotransferase level and microsomal lipid peroxidation were markedly increased by ischemia/reperfusion. These increases were significantly attenuated by rebamipide, α-tocopherol or allopurinol. Bile flow and cholate output were markedly decreased by ischemia/reperfusion and free radical scavengers, especially rebamipide, restored their secretion. **NADPH**-cytochrome P450 **reductase** activity and cytochrome P450 content were decreased by ischemia/reperfusion. Rebamipide prevented the decrease of the **NADPH**-cytochrome P450 **reductase** activity but had little effect on the cytochrome P450 content. Aminopyrine N-demethylase activity was decreased and aniline p-hydroxylase was increased by **ischemia /reperfusion**, which were **prevented** by α-tocopherol and allopurinol, but not by rebamipide. Our findings suggest that ischemia/reperfusion diminishes hepatic secretory function and microsomal function by increasing lipid peroxidation, and rebamipide significantly ameliorates these changes through its free radical scavenging activity.
CT Medical Descriptors:
*liver dysfunction
*liver ischemia
*reperfusion injury
aminotransferase blood level
animal experiment
animal model
animal tissue
article
bile secretion

controlled study
drug metabolism
intraperitoneal drug administration
lipid peroxidation
liver microsome
male
nonhuman
oral drug administration
priority journal
rat
Drug Descriptors:
*proamipide: PD, pharmacology
*proamipide: CM, drug comparison
*scavenger: CM, drug comparison
*scavenger: PD, pharmacology
allopurinol: PD, pharmacology
allopurinol: CM, drug comparison
alpha tocopherol: PD, pharmacology
alpha tocopherol: CM, drug comparison
aminopyrine n demethylase: EC, endogenous compound
aminotransferase: EC, endogenous compound
cholic acid: EC, endogenous compound
cytochrome p450: EC, endogenous compound
free radical: EC, endogenous compound
malonaldehyde: EC, endogenous compound
reduced nicotinamide adenine dinucleotide ferrihemoprotein reductase: EC, endogenous compound
unspecific monooxygenase: EC, endogenous compound
RN (proamipide) 111911-87-6; (allopurinol) 315-30-0; (alpha tocopherol) 1406-18-4, 1406-70-8, 52225-20-4, 58-95-7, 59-02-9; (aminopyrine n demethylase) 9037-69-8; (aminotransferase) 9031-66-7; (cholic acid) 32500-01-9, 361-09-1, 81-25-4; (cytochrome p450) 9035-51-2; (malonaldehyde) 542-78-9; (unspecific monooxygenase) 9012-80-0, 9037-52-9, 9038-14-6

L161 ANSWER 98 OF 127 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 95263431 EMBASE
DOCUMENT NUMBER: 1995263431
TITLE: Myocardial and endothelial protection by TMS in ischemia-reperfusion injury.
AUTHOR: Murohara T.; Buerke M.; Margiotta J.; Ruan F.; Igarashi Y.; Hakomori - S.I.; Lefer A.M.
CORPORATE SOURCE: Dept. of Physiology, Jefferson Medical College, Thomas Jefferson Univ., 1020 Locust St.,Philadelphia, PA 19107-6799, United States
SOURCE: American Journal of Physiology - Heart and Circulatory Physiology, (1995) Vol. 269, No. 2 38-2, pp. H504-H514. . ISSN: 0363-6135 CODEN: AJPPDI
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 26 Sep 1995
Last Updated on STN: 26 Sep 1995
ED Entered STN: 26 Sep 1995
Last Updated on STN: 26 Sep 1995

AB N,N,N-**trimethylsphingosine** (TMS), a stable synthetic **sphingosine** derivative, was investigated in a feline model of myocardial ischemia (90 min) and reperfusion (270 min) injury. TMS (60 μg/kg), **administered** intravenously 10 min before **reperfusion**, significantly attenuated myocardial necrosis (15 ± 3 vs. 31 ± 4% necrosis of area at risk, P < 0.01) and cardiac myeloperoxidase activities, a marker of neutrophil accumulation, compared with vehicle-treated cats. Endothelium-dependent relaxation to acetylcholine in **ischemic-reperfused** coronary artery rings **treated** with TMS was also significantly preserved compared with vehicle (73 ± 4 vs. 34 ± 4% vasorelaxation, P < 0.01). Polymorphonuclear neutrophil (PMN) adherence to coronary endothelium 270 min after **reperfusion** was markedly attenuated in the TMS group compared with vehicle-**treated** cats (37 ± 5 vs. 76 ± 5 PMN/mm2, P < 0.01). TMS also attenuated upregulation of P-selectin on coronary venular endothelium by immunohistochemistry. This was consistent with in vitro findings that TMS attenuates PMN adherence to thrombin-stimulated coronary endothelium and P-selectin upregulation on thrombin-stimulated cat platelets. A **sphingolipid** derivative, TMS at physiological concentrations exerts cardioprotective actions and preserves coronary endothelial function following myocardial ischemia and reperfusion in vivo. The effects appear to be mediated by the inhibition of PMN-endothelial interaction and subsequent accumulation into the ischemic myocardium. Thus TMS may be a useful agent in attenuating myocardial reperfusion injury.

CT Medical Descriptors:
*cell death
*heart muscle reperfusion
*reperfusion injury: ET, etiology
animal cell
animal model
article
cat
cell protection
controlled study
coronary artery circumflex branch
coronary artery dilatation
heart protection
intravenous drug administration
left anterior descending coronary artery
leukocyte adherence inhibition
male
neutrophil
nonhuman
priority journal
vascular endothelium
Drug Descriptors:
***sphingosine derivative: DO, drug dose**
***sphingosine derivative: PD, pharmacology**
15 hydroxy 11alpha,9alpha epoxymethanoprosta 5,13 dienoic acid: CM, drug comparison
15 hydroxy 11alpha,9alpha epoxymethanoprosta 5,13 dienoic acid: DO, drug dose
15 hydroxy 11alpha,9alpha epoxymethanoprosta 5,13 dienoic acid: PD, pharmacology
acetylcholine: DO, drug dose
acetylcholine: CM, drug comparison
acetylcholine: PD, pharmacology
calcimycin: CM, drug comparison
calcimycin: DO, drug dose

calcimycin: PD, pharmacology
myeloperoxidase: EC, endogenous compound
n,n,n trimethylsphingosine: DO, drug dose
n,n,n trimethylsphingosine: PD, pharmacology
padgem protein: EC, endogenous compound
phorbol 13 acetate 12 myristate: DO, drug dose
phorbol 13 acetate 12 myristate: PD, pharmacology
sodium nitrate: CM, drug comparison
sodium nitrate: DO, drug dose
sodium nitrate: PD, pharmacology
superoxide: EC, endogenous compound
superoxide dismutase: DO, drug dose
superoxide dismutase: PD, pharmacology
unclassified drug
RN (15 hydroxy 11alpha,9alpha epoxymethanoprosta 5,13 dienoic acid) 56985-40-1; (acetylcholine) 51-84-3, 60-31-1, 66-23-9; (calcimycin) 52665-69-7; (phorbol 13 acetate 12 myristate) 16561-29-8; (sodium nitrate) 7631-99-4; (superoxide) 11062-77-4; (superoxide dismutase) 37294-21-6, 9016-01-7, 9054-89-1
CN A 23187; U 46619

L161 ANSWER 99 OF 127 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 94368838 EMBASE
DOCUMENT NUMBER: 1994368838
TITLE: Gangliosides - A new **therapeutic** agent against **stroke** and Alzheimer's disease.
AUTHOR: Svennerholm L.
CORPORATE SOURCE: Department of Clinical Neuroscience, University of Goteborg, Monlndal Hospital,S-431 80 Molndal, Sweden
SOURCE: Life Sciences, (1994) Vol. 55, No. 25-26, pp. 2125-2134. . ISSN: 0024-3205 CODEN: LIFSAK
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 12 Jan 1995
Last Updated on STN: 12 Jan 1995
ED Entered STN: 12 Jan 1995
Last Updated on STN: 12 Jan 1995
AB Gangliosides are **glycosphingolipids** localized to the outer leaflet of the plasma membrane of vertebrate cells. The highest ganglioside concentration of any organ is found in the mammalian brain, where the gangliosides are enriched in the neuronal membrane, particularly in the synapses. There are four major brain gangliosides with the same neutral tetrasaccharide core to which one to three sialic acids are linked - the simplest being the GM1-ganglioside. These gangliosides have been shown to have neuritogenic and neuronotrophic activity and to facilitate repair of neuronal tissue after mechanical, biochemical or toxic injuries. Mixtures of native bovine brain gangliosides were adopted for pharmacological use in the treatment of peripheral nerve damage, and GM1-ganglioside has been applied for the treatment of CNS injuries and diseases. Beneficial effects of GM1 have been documented in the **treatment** of **stroke** and spinal cord injuries, particularly when the **treatment** has been initiated within a few hours of the acute event. Continuous intraventricular infusion of GM1 has

recently been shown to have a significant beneficial effect in Alzheimer disease of early onset (AD Type I).

CT Medical Descriptors:
*alzheimer disease: ET, etiology
*alzheimer disease: DT, drug therapy
*stroke: DT, drug therapy
*stroke: ET, etiology
animal model
brain
cell growth
cell membrane
cell regeneration
clinical trial
conference paper
human
nerve cell lesion
nonhuman
spinal cord injury: DT, drug therapy
spinal cord injury: ET, etiology
synapse
Drug Descriptors:
*ganglioside: EC, endogenous compound
*ganglioside: DT, drug therapy
*ganglioside: PD, pharmacology
*ganglioside gm1: PD, pharmacology
*ganglioside gm1: EC, endogenous compound
*ganglioside gm1: DT, drug therapy
RN (ganglioside gm1) 37758-47-7

L161 ANSWER 100 OF 127 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 93060091 EMBASE
DOCUMENT NUMBER: 1993060091
TITLE: (+)-Hemipalmitoylcarnitinium strongly inhibits carnitine **palmitoyltransferase**-I in intact mitochondria.
AUTHOR: Gandour R.D.; Leung O.-T.; Greway A.T.; Ramsay R.R.; A' Bhaird N.N.; Fronczek F.R.; Bellard B.M.; Kumaravel G.
CORPORATE SOURCE: Department of Chemistry, Louisiana State University,Baton Rouge, LA 70803-1804, United States
SOURCE: Journal of Medicinal Chemistry, (1993) Vol. 36, No. 2, pp. 237-242. .
ISSN: 0022-2623 CODEN: JMCMAR
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 4 Apr 1993
Last Updated on STN: 4 Apr 1993
ED Entered STN: 4 Apr 1993
Last Updated on STN: 4 Apr 1993
AB The reaction of the methyl ester of (R)-norcarnitine with 1-bromo-2-heptadecanone produces (+)-6-[(methoxycarbonyl)methyl]-2-pentadecyl-4,4-dimethylmorpholinium bromide, 3, which hydrolyzes to (+)-6-(carboxylatomethyl)-2-pentadecyl-4,4-dimethylmorpholinium (hemipalmitoylcarnitinium, HPC) upon treatment with aqueous sodium hydroxide. Single-crystal X-ray analyses have confirmed the structures of (+)-HPC and 3. (+)-HPC inhibits carnitine **palmitoyltransferase** (CPT-I) activity for the forward reaction (palmitoyl-CoA + carnitine

→) in intact mitochondria from rat heart and rat liver. (+)-HPC competitively (versus carnitine) inhibits CPT-I activity in both rat heart and liver mitochondria with K(i) = 2.8 ± 0.5 and 4.2 ± 0.7 μM, respectively. As one of the strongest specific inhibitors of CPT-I, HPC is a potential **therapeutic** agent in myocardial **ischemia** and Type II diabetes.

CT Medical Descriptors:
*enzyme inhibition
*enzyme kinetics
article
competitive inhibition
enzyme mechanism
heart mitochondrion
heart muscle ischemia
inhibition kinetics
liver mitochondrion
non insulin dependent diabetes mellitus
priority journal
structure analysis
X ray crystallography
Drug Descriptors:
*acyltransferase inhibitor: AN, drug analysis
*acyltransferase inhibitor: DV, drug development
*acyltransferase inhibitor: PD, pharmacology
***carnitine palmitoyltransferase: EC, endogenous compound**
hemipalmitoylcarnitinium: AN, drug analysis
hemipalmitoylcarnitinium: DV, drug development
hemipalmitoylcarnitinium: PD, pharmacology
unclassified drug

RN (carnitine **palmitoyltransferase**) 9068-41-1

L161 ANSWER 101 OF 127 EMBASE

ACCESSION NUMBER: 93008306 EMBASE
DOCUMENT NUMBER: 1993008306
TITLE: Evidence that **NADPH**-dependent methemoglobin **reductase** and administered riboflavin protect tissues from oxidative injury.
AUTHOR: Hultquist D.E.; Quandt K.S.; Shlafer M.; Mack C.P.; Till G.O.; Seekamp A.; Betz A.L.; Ennis S.R.; Xu F.
CORPORATE SOURCE: Department of Biological Chemistry, University of Michigan,Ann Arbor, MI 48109-0606, United States
SOURCE: American Journal of Hematology, (1993) Vol. 42, No. 1, pp. 13-18. .
ISSN: 0361-8609 CODEN: AJHEDD
COUNTRY: United States
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 025 Hematology
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 24 Jan 1993
Last Updated on STN: 24 Jan 1993

ED Entered STN: 24 Jan 1993
Last Updated on STN: 24 Jan 1993

AB **NADPH**-dependent methemoglobin **reductase**, first detected in erythrocytes sixty years ago, has subsequently been purified and characterized as a methylene blue reductase and a flavin reductase. The reductase plays no role in methemoglobin reduction under normal

conditions, but its activity serves as the basis for the treatment of methemoglobinemia with methylene blue or flavin. On-going studies demonstrate that this cytosolic protein is also present in liver and that its primary structure distinguishes it from other known proteins. The bovine erythrocyte reductase tightly binds hemes, porphyrins, and fatty acids with resulting loss of activity. Pyrroloquinoline quinone serves as a high-affinity substrate of the reductase, suggesting that this naturally-occurring compound may be a physiological substrate. The ability of the reductase to catalyze the intracellular reduction of administered riboflavin to dihydroriboflavin suggested that this system might be exploited to protect tissues from oxidative damage. This hypothesis was supported by our finding that dihydroriboflavin reacts rapidly with Fe(IV)O and Fe(V)O oxidation states of hemeproteins, states that have been implicated in tissue damage associated with ischemia and reperfusion. Preliminary studies demonstrate that, as predicted, **administration** of low concentrations of riboflavin protects isolated rabbit **heart** from reoxygenation **injury**, rat lung from **injury** resulting from systemic activation of complement, and rat brain from damage caused by four hours of ischemia. Data from these animal studies suggest that flavin **therapy** holds promise in protecting tissue from the oxidative **injuries** of **myocardial** infarction, acute lung **injury**, stroke, and a number of other clinical conditions.

CT Medical Descriptors:
*methemoglobinemia: ET, etiology
*methemoglobinemia: DT, drug therapy
*tissue injury
human
intraperitoneal drug administration
priority journal
short survey
Drug Descriptors:
*methemoglobin: EC, endogenous compound
*methemoglobin reductase: EC, endogenous compound
*reduced nicotinamide adenine dinucleotide phosphate: EC, endogenous compound
*riboflavin: PD, pharmacology
*riboflavin: DT, drug therapy

RN (methemoglobin reductase) 9032-80-8; (reduced nicotinamide adenine dinucleotide phosphate) 53-57-6; (riboflavin) 83-88-5

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ACCESSION NUMBER: 92368042 EMBASE
DOCUMENT NUMBER: 1992368042
TITLE: The relative contribution of glucose and fatty acids to ATP production in hearts reperfused following ischemia.
AUTHOR: Lopaschuk G.D.; Saddik M.
CORPORATE SOURCE: 423 Heritage Medical Research Bldg., University of Alberta,Edmonton, Alta. T6G 2S2, Canada
SOURCE: Molecular and Cellular Biochemistry, (1992) Vol. 116, No. 1-2, pp. 111-116. .
ISSN: 0300-8177 CODEN: MCBIB8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 10 Jan 1993
Last Updated on STN: 10 Jan 1993
ED Entered STN: 10 Jan 1993
Last Updated on STN: 10 Jan 1993
AB High levels of fatty acids decrease the extent of mechanical recovery of hearts reperfused following a transient period of severe ischemia. Glucose oxidation rates during reperfusion are low under these conditions, which can result in a decreased recovery of mechanical function. Stimulation of glucose oxidation with the carnitine **palmitoyl transferase** I inhibitor. Etomoxir, or by directly stimulating pyruvate dehydrogenase activity with dichloroacetate (DCA) results in an improvement in mechanical function during reperfusion of previously ischemic hearts. Addition of DCA (1 mM) to hearts perfused with 11 mM glucose and 1.2 mM palmitate results in an increase in contribution of glucose oxidation to overall ATP production from 6 to 23%, with a parallel decrease in that of fatty acid oxidation from 90 to 69%. In aerobic hearts, endogenous myocardial triglycerides are an important source of fatty acids for β-oxidation. Using hearts in which the myocardial triglycerides were pre-labeled, the contribution of both endogenous and exogenous fatty acid oxidation to myocardial ATP production was determined in hearts perfused with 11 mM glucose, 1.2 mM palmitate and 500 μU/ml insulin. In hearts reperfused following a 30 min period of global no flow ischemia, 91.9% of ATP production was derived from endogenous and exogenous fatty acid oxidation, compared to 87.7% in aerobic hearts. This demonstrates that fatty acid oxidation quickly recovers following a transient period of severe ischemia. Furthermore, **therapy** aimed at overcoming fatty acid inhibition of glucose oxidation during **reperfusion** of ischemic hearts appears to be beneficial to recovery of mechanical function.
CT Medical Descriptors:
*fatty acid oxidation
*glucose oxidation
*heart muscle ischemia
*heart muscle reperfusion
aerobic metabolism
animal tissue
article
cell energy
glucose utilization
glycolysis
isolated heart
male
nonhuman
priority journal
rat
Drug Descriptors:
*adenosine triphosphate: EC, endogenous compound
*fatty acid: EC, endogenous compound
*glucose: EC, endogenous compound
carnitine palmitoyltransferase: EC, endogenous compound
dichloroacetic acid
etomoxir: PD, pharmacology
insulin
palmitic acid
pyruvate dehydrogenase: EC, endogenous compound
RN (adenosine triphosphate) 15237-44-2, 56-65-5, 987-65-5; (glucose) 50-99-7, 84778-64-3; (carnitine **palmitoyltransferase**) 9068-41-1; (dichloroacetic acid) 13425-80-4, 2156-56-1, 79-43-6; (etomoxir) 82258-36-4; (insulin) 9004-10-8; (palmitic acid) 57-10-3; (pyruvate dehydrogenase) 9014-20-4

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ACCESSION NUMBER: 91350993 EMBASE
DOCUMENT NUMBER: 1991350993
TITLE: Muscle carnitine deficiency in patients with severe peripheral vascular disease.
AUTHOR: Brevetti G.; Angelini C.; Rosa M.; Carrozzo R.; Perna S.; Corsi M.; Matarazzo A.; Marcialis A.
CORPORATE SOURCE: Via G. Iannelli 45/A,80131 Napoli, Italy
SOURCE: Circulation, (1991) Vol. 84, No. 4, pp. 1490-1495. .
ISSN: 0009-7322 CODEN: CIRCAZ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Mar 1992
Last Updated on STN: 16 Mar 1992

ED Entered STN: 16 Mar 1992
Last Updated on STN: 16 Mar 1992

AB Background. This study was designed to evaluate the effect of severe peripheral arterial insufficiency on carnitine concentrations and carnitine acetyltransferase and **palmitoyltransferase** activities in the ischemic skeletal muscles of patients with severe peripheral vascular disease. Methods and Results. Nine biopsy specimens of ischemic muscles were obtained from five patients undergoing reconstructive vascular surgery. Biopsies from 35 normal subjects served as controls. Ischemic muscles showed a significant reduction in total carnitine from the control value of 20.9±5.2 to 11.6±6.2 nmol/mg noncollagen protein ($p<0.01$). A significantly lower free carnitine and acylcarnitine content contributed to this reduction. Similarly, carnitine acetyltransferase activity was reduced in the ischemic muscles from the control value of 102.1±41.2 to 52.9±22.1 nmol/min/mg noncollagen protein ($p<0.01$). On the contary, carnitine **palmitoyltransferase** activity did not show any change (0.29±0.05 nmol/min/mg noncollagen protein in the ischemic muscles and 0.28±0.07 nmol/min/mg noncollagen protein in controls). Carnitine, acylcarnitines, and enzyme activities were also measured in the **ischemic** muscles in four additional patients 2 days after intravenous **administration** of L-propionylcarnitine (1.5 g as a single bolus followed by an infusion of 1 mg/kg/min for 30 minutes). **Treatment** restored normal levels of carnitine and its esters in the **ischemic** muscles but did not affect enzyme activities. Conclusions. Demonstration of carnitine deficiency in severe peripheral vascular disease substantiates previous findings showing the efficacy of carnitine supplementation to ischemic muscles. Furthermore, the feasibility of restoring carnitine homeostasis with L-propionylcarnitine provides the basis for clinical trials aimed at assessing the efficacy of this carnitine ester in the treatment of peripheral vascular disease.

CT Medical Descriptors:
*peripheral vascular disease: DI, diagnosis
*peripheral vascular disease: SU, surgery
*peripheral vascular disease: DT, drug therapy
*skeletal muscle
adult
aged
article

clinical article
controlled study
histochemistry
human
human tissue
intravenous drug administration
priority journal
Drug Descriptors:
*carnitine: EC, endogenous compound
*propionylcarnitine: PD, pharmacology
carnitine acyltransferase: EC, endogenous compound
RN (carnitine) 461-06-3, 541-15-1, 56-99-5; (propionylcarnitine) 17298-37-2; (carnitine acyltransferase) 39386-49-7

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ACCESSION NUMBER: 91125940 EMBASE
DOCUMENT NUMBER: 1991125940
TITLE: Carnitine **palmitoyltransferase** in cardiac ischemia. A potential site for altered fatty acid metabolism.
AUTHOR: Pauly D.F.; Kirk K.A.; McMillin J.B.
CORPORATE SOURCE: Dept. Pathology/Lab. Medicine, University of Texas, Medical School, 6431 Fannin Street,Houston, TX 77030, United States
SOURCE: Circulation Research, (1991) Vol. 68, No. 4, pp. 1085-1094.
.
ISSN: 0009-7330 CODEN: CIRUAL
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Dec 1991
Last Updated on STN: 16 Dec 1991
ED Entered STN: 16 Dec 1991
Last Updated on STN: 16 Dec 1991
AB The sensitivity of carnitine palmitoyl coenzyme A (CoA) transferase I to inhibition of its activity by malonyl-CoA is progressively reduced in mitochondria isolated from ischemic cardiac cells as blood flow decreases to 30% or less of the preocclusion flow. The activity of carnitine **palmitoyl**-CoA **transferase** I in mitochondria isolated from nonischemic cardiac cells demonstrates incomplete inhibition, even at high concentrations of malonyl-CoA. Kinetic analyses of these data gave results most consistent with the expression of two overt enzyme activities: one activity that is sensitive to inhibition by malonyl-CoA and one activity that demonstrates little or no sensitivity to such inhibition. The decrease in malonyl-CoA-sensitive activity associated with ischemia results from a 13% decrease in the activity of the sensitive component and a corresponding 13% increase in the activity of the insensitive component. Decreased sensitivity of ischemic carnitine **palmitoyl**-CoA **transferase** I to inhibition by malonyl-CoA, together with potential fluctuations in the content of malonyl-CoA in tissue, would increase the synthesis of palmitoylcarnitine during ischemia and facilitate return to the use of fatty acid as a preferred metabolic fuel on reperfusion. This apparent conversion occurs concomitantly with a decrease in the free protein thiol content of the mitochondrial membranes isolated from ischemic cardiac cells. **Treatment** of the mitochondria from **ischemic** cardiac cells with dithiothreitol in vitro partially reverses the loss in

sensitivity to malonyl-CoA, suggesting the possible role of thiol oxidation in the altered metabolism of ischemic mitochondria. Western blot analysis of these mitochondria using an antibody against carnitine **palmitoyltransferase** II purified from beef heart demonstrates a 68-kDa protein, which under ischemic conditions apparently is decreased by 2 kDa. These results are more indicative of a modification in protein folding of carnitine **palmitoyltransferase** than proteolytic changes during ischemia.

CT Medical Descriptors:
*heart muscle ischemia
*mitochondrion
*protein degradation
animal experiment
animal tissue
article
controlled study
dog
nonhuman
priority journal
Drug Descriptors:
***carnitine palmitoyltransferase: EC, endogenous compound**
*dithiothreitol
*malonyl coenzyme a

RN (carnitine **palmitoyltransferase**) 9068-41-1; (dithiothreitol) 3483-12-3; (malonyl coenzyme a) 524-14-1

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ACCESSION NUMBER: 91126311 EMBASE
DOCUMENT NUMBER: 1991126311
TITLE: Amphipathic lipid metabolites and their relation to arrhythmogenesis in the ischemic heart.
AUTHOR: DaTorre S.D.; Creer M.H.; Pogwizd S.M.; Corr P.B.
CORPORATE SOURCE: Cardiovascular Division, Department of Medicine, Washington Univ School of Med, 660 South Euclid Avenue,St. Louis, MO 63110, United States
SOURCE: Journal of Molecular and Cellular Cardiology, (1991) Vol. 23, No. SUPPL. 1, pp. 11-22. .
ISSN: 0022-2828 CODEN: JMCDAY
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Dec 1991
Last Updated on STN: 16 Dec 1991

ED Entered STN: 16 Dec 1991
Last Updated on STN: 16 Dec 1991

AB Myocardial ischemia is associated with profound electrophysiologic derangements which occur within minutes and are rapidly reversible with reperfusion, suggesting that subtle and reversible biochemical alterations within or near the sarcolemma contribute. Our efforts have concentrated on two structurally similar amphipathic metabolites, long-chain acylcarnitine and lysophosphatidylcholine. Studies performed in vitro in isolated tissue indicate that incorporation of either metabolite into the sarcolemma at concentrations of 1-2 mole %, as verified using electron microscopic (EM) autoradiography, elicits profound electrophysiologic derangements analogous to those seen in the ischemic heart in vivo. In isolated myocytes in vitro, the electrophysiologic derangements elicited by hypoxia are associated with a marked 70-fold increase in the endogenous

sarcolemmal accumulation of long-chain acylcarnitine. Inhibition of carnitine acyltransferase I (CAT-I) not only prevents the accumulation of long-chain acylcarnitine in isolated myocytes exposed to severe hypoxia, but also markedly attenuates the electrophysiologic alterations. Several lines of experimental evidence, including measurements in venous effluents as well as cardiac lymph, indicate that lysophosphatidylcholine (LPC) accumulates to a large extent in the extracellular space during ischemia. This extracellular accumulation may be secondary to release from vascular endothelium, smooth muscle or blood cell elements. In crude homogenates of myocardial tissue, the total enzymic activity for catabolism of LPC far exceeds the total activity for synthesis of LPC mediated by phospholipase A2 (PLA2) catalyzed hydrolysis of phosphatidylcholine (PC). Therefore, inhibition of catabolism would be required for net accumulation of LPC to occur. Three enzymes responsible for the catabolism of LPC are inhibited by either long-chain acylcarnitine or acidic pH. Thus, accumulation of long-chain acylcarnitine and acidosis contribute to the increase in LPC observed in ischemic tissue. In this report, we provide evidence that accumulation of long-chain acylcarnitine occurs very rapidly in ischemic myocardium in vivo, coincident with the development of electrophysiologic alterations leading to malignant arrhythmias as verified using 3-dimensional cardiac mapping procedures. Following a brief, 2-min period of ischemia, long-chain acylcarnitine content increased four-fold in the ischemic region, concomitant with the development of electrophysiologic abnormalities observed during this period. Additionally, we demonstrate that modification of intracellular lipolysis by β-adrenergic receptor stimulation or blockade does not influence long-chain acylcarnitine accumulation following this 2-min interval of ischemia. These results suggest that production of long-chain acylcarnitine is not limited by the intracellular free fatty acid concentration early in ischemia. Inhibition of CAT-I prevents not only the accumulation of long-chain acylcarnitine but also the accumulation of LPC and the occurrence of ventricular tachycardia or fibrillation during a 5-min ischemic interval. These results indicate that inhibition of CAT-I may be a promising **therapeutic** strategy to modify the incidence of lethal arrhythmias associated with **ischemic** heart disease in man.

CT Medical Descriptors:
*heart arrhythmia
*heart muscle ischemia
*lipid metabolism
conference paper
priority journal
Drug Descriptors:
*acylcarnitine
*carnitine
***carnitine palmitoyltransferase**

RN (carnitine) 461-06-3, 541-15-1, 56-99-5; (carnitine **palmitoyltransferase**) 9068-41-1

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ACCESSION NUMBER: 89242706 EMBASE
DOCUMENT NUMBER: 1989242706
TITLE: Metabolic oxidation of glucose during early myocardial reperfusion.
AUTHOR: Renstrom B.; Nellis S.H.; Liedtke A.J.
CORPORATE SOURCE: Section of Cardiology, University of Wisconsin, Madison, WI 53792, United States
SOURCE: Circulation Research, (1989) Vol. 65, No. 4, pp. 1094-1101.
.
ISSN: 0009-7330 CODEN: CIRUAL

COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 12 Dec 1991
Last Updated on STN: 12 Dec 1991
ED Entered STN: 12 Dec 1991
Last Updated on STN: 12 Dec 1991

AB We have previously studied the relation between long-chain fatty acid and pyruvate metabolism in reperfused myocardium and noted a rapid return of fatty acid oxidation to at least preischemic values accompanied by a marked decrease in pyruvate oxidation. The purpose of the present report is to further characterize carbohydrate metabolism during reflow by describing rates of glucose oxidation using [6-14C]glucose. Oxidative performance was determined with and without preserved fatty acid utilization; the latter condition was effected by oxfenicine, which inhibits **palmitoylcarnitine transferase** I. In the main protocol, two groups of working swine hearts (n = 18) were perfused aerobically for 30 minutes, rendered regionally ischemic (-60 Δ% in anterior descending coronary flow) for 45 minutes, and reperfused at control flows for a final 50 minutes of perfusion. An emulsion of Intralipid with heparin was administered systemically throughout the studies to augment serum fatty acids (average fatty acid values, 1.05 ± 0.05 μmol/ml for both groups). Serum glucose was monitored and maintained at or about 100 mg/dl with additional infusions of glucose as needed. Oxfenicine (33 mg/kg) was administered systemically by bolus injection at time 0 and 60 minutes of perfusion in nine animals. Decreased mechanical performance, that is, stunning, during reflow was evident in both groups (-50 Δ% in regional systolic shortening, $p \leq 0.05$ compared with aerobic values in the control group, and -32 Δ%, $p \leq 0.05$ compared with aerobic values in treated hearts). This stunning was associated with concordant reductions in myocardial oxygen consumption during recovery (-15 Δ%, $p \leq 0.02$ for the control group, and -21 Δ%, $p \leq 0.01$ for the treated group). 14CO2 production from labeled glucose was strongly suppressed during preischemic perfusion in both groups, rose slightly during ischemia, and continued to rise in the oxfenicine group during reperfusion to twice the values measured in control hearts ($p \leq 0.01$). These responses were contrasted with data from five additional, similarly perfused hearts that did not receive Intralipid. Reducing fatty acids twofold in the perfusate caused no major changes in glucose oxidation as compared with control hearts. Tissue glycogen was detected in both aerobic and **reperfused** myocardium and was unaffected by oxfenicine **treatment.** These data confirm previous findings and do not support an argument for increased glucose oxidation. Rather, the results support the concept of competitive inhibition of glucose and/or its intermediates by the preferred use of fatty acids.

CT Medical Descriptors:
*heart muscle ischemia: ET, etiology
*heart muscle metabolism
*reperfusion
swine
animal cell
nonhuman
priority journal
Drug Descriptors:
*fatty acid
*glucose
RN (glucose) 50-99-7, 84778-64-3

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ACCESSION NUMBER: 89134561 EMBASE
DOCUMENT NUMBER: 1989134561
TITLE: Acute arthropod envenomation. Incidence, clinical features and management.
AUTHOR: Binder L.S.
CORPORATE SOURCE: Division of Emergency Medicine, Texas Tech University Regional Academic Health Center, El Paso, TX 79905, United States
SOURCE: Medical Toxicology and Adverse Drug Experience, (1989) Vol. 4, No. 3, pp. 163-173. .
ISSN: 0113-5244 CODEN: METOEV
COUNTRY: New Zealand
DOCUMENT TYPE: Journal
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
052 Toxicology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 12 Dec 1991
Last Updated on STN: 12 Dec 1991

ED Entered STN: 12 Dec 1991
Last Updated on STN: 12 Dec 1991

AB Black widow spider (Latrodectus mactans) envenomation is found throughout both the temperate and tropical latitudes, and is one of the leading causes of death from arthropod envenomations worldwide. The venom is highly neurotoxic, affecting the presynaptic motor endplate to allow massive noradrenaline (norepinephrine) and acetylcholine release into synapses causing excessive stimulation and fatigue of the motor end plate and muscle. Clinically, patients develop a bite site lesion and pain, abdominal pain and tenderness, and lower extremity pain and weakness within minutes to hours of envenomation. Symptoms progress over several hours, then subside over 2 to 3 days. The recommended treatment of 'common' envenomation is calcium gluconate 10% intravenously, titrated to relief of symptoms; antivenin, although effective, may cause hypersensitivity and serum sickness reactions, and should be restricted to life-threatening envenomations only. Brown recluse spider (Loxosceles reclusa) envenomations are seen in the Americas and in Europe, and are endemic to the south and central United States. The venom contains at least 8 enzymes, consisting of various lysins (facilitating venom spread) and **sphingo**-myelinase D, which **causes** cell membrane injury and lysis, thrombosis, local **ischaemia**, and chemotaxis. Local envenomations begin as pain and itching that progresses to vesiculation with violaceous necrosis and surrounding erythema, and ultimately ulcer formation. Systemic envenomations may be life threatening, and present with fever, constitutional symptoms, petechial eruptions, thrombocytopenia, and haemolysis with haemoglobinuric renal failure. Treatment of local envenomations is conservative (local wound care, cryotherapy, elevation, tetanus prophylaxis, and close follow-up); systemic envenomation requires supportive care and treatment of arising complications, corticosteroids to stabilise red blood cell membranes, and support of renal function. Dapsone 100 mg daily has emerged as a promising therapeutic agent in both animal studies and clinical trials. Over 650 species of scorpions are known to cause envenomation (mostly in children under 10 years); they are endemic mostly in arid and tropical areas. Different venoms and clinical presentations are seen across the different species. Most commonly, an inflammatory local reaction occurs with envenomation, which is treated with wound debridement and cleansing,

tetanus prophylaxis, and antihistamines. Occasionally the venom is allergenic, and the resultant allergic reaction is treated in a standard fashion. Infrequently, Centruroides sculpturatus may cause a severe cholinergic envenomation, with presentation of severe cholinergic toxicity (salivation, lacrimation, urination, defecation, bradycardia, bronchospasm, fasciculations). These patients need intensive care unit milieu, treatment of bronchospasm, and high dose anticholinergic therapy titrated to relief of symptoms.

CT Medical Descriptors:
*arthropod
*envenomation: DT, drug therapy
short survey
human
Drug Descriptors:
*scorpion venom
*spider venom
*antibiotic agent: DT, drug therapy
*antihistaminic agent: DT, drug therapy
*bronchodilating agent: DT, drug therapy
*cholinergic receptor blocking agent: DT, drug therapy
*corticosteroid: DT, drug therapy
*venom antiserum: DT, drug therapy
adrenalin
aminophylline
atropine
dapsone
gluconate calcium
phenobarbital

RN (adrenalin) 51-43-4, 55-31-2, 6912-68-1; (aminophylline) 317-34-0; (atropine) 51-55-8, 55-48-1; (dapsone) 80-08-0; (gluconate calcium) 299-28-5; (phenobarbital) 50-06-6, 57-30-7, 8028-68-0

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ACCESSION NUMBER: 89158645 EMBASE
DOCUMENT NUMBER: 1989158645
TITLE: Gangliosides in treatment of neural injury and disease.
AUTHOR: Mahadik S.P.; Karpiak S.K.
CORPORATE SOURCE: Department of Biochemistry, College of Physicians and Surgeons, Columbia University, New York, NY 10032, United States
SOURCE: Drug Development Research, (1988) Vol. 15, No. 4, pp. 337-360. .
ISSN: 0272-4391 CODEN: DDREDK
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 12 Dec 1991
Last Updated on STN: 12 Dec 1991

ED Entered STN: 12 Dec 1991
Last Updated on STN: 12 Dec 1991

AB Gangliosides are being used therapeutically to **treat** a variety of nervous system disorders including peripheral neuropathies and **stroke.** Gangliosides (over 70 molecular species) are **glycosphingolipids** found in highest concentrations in neural tissue. They are thought to be functional in such diverse biological

processes as embryogenesis and cell death, and specifically in membrane-mediated processes (cell-cell interactions, ionic balance, synaptic transmission, and receptor-mediated information transfer). Their distribution changes during neural development, indicative of differential roles for each molecular species at critical stages of development. Ganglioside distribution differs during abnormal development or after neural injury due to trauma or disease. In vivo and in vitro studies have shown that exogenous gangliosides can substitute (structurally and functionally) for the endogenous molecules. This has made it possible to investigate the molecular mechanisms of ganglioside function in situ. During the genesis of these studies it became clear that exogenous gangliosides were able to protect the chemical and morphological changes associated with neural (CNS and PNS) tissue injury (mechanical, ischemic, and neurotoxic). This protective effect has been characterized by facilitated functional recovery in a number of CNS injury paradigms. The mechanism(s) for the facilitative effect of ganglioside treatment is unidentified. Data support a number of hypotheses. One contends that gangliosides can acutely reduce the extent of CNS injury and pathology by protection of membrane structure/function, thereby leading to reduced functional deficits and therefore to increased potential for functional recovery. Another hypothesis supports the view that these **glycosphingolipids** may **promote** neuronal regeneration through **modulation** of trophic factors. Studying the effects of exogenous gangliosides on CNS injury is leading to further insight into the critical functions of endogenous gangliosides as well as focusing attention on the potential of exogenous gangliosides as a therapeutic treatment of traumatic and degenerative CNS disorders.

CT Medical Descriptors:
*brain level
*brain region
*development
*nerve lesion
*neuropathy
*stroke
cytology
injury
rat
review
clinical article
animal experiment
animal cell
human
nonhuman
intramuscular drug administration
subcutaneous drug administration
priority journal
Drug Descriptors:
*ganglioside: PD, pharmacology
*ganglioside: AN, drug analysis
*ganglioside: DV, drug development
*ganglioside: CR, drug concentration
*ganglioside gm1

RN (ganglioside gm1) 37758-47-7

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ACCESSION NUMBER: 88027242 EMBASE
DOCUMENT NUMBER: 1988027242
TITLE: Carnitine-acylcarnitine translocase in ischemia: Evidence for sulfhydryl modification.

AUTHOR: Pauly D.F.; Yoon S.B.; McMillin J.B.
CORPORATE SOURCE: Section of Cardiovascular Sciences, Department of Medicine, Baylor College of Medicine, Houston, TX 77030, United States
SOURCE: American Journal of Physiology - Heart and Circulatory Physiology, (1987) Vol. 253/6 (22, No. 6), pp. H1557-H1565.
.
ISSN: 0002-9513 CODEN: AJPPDI
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 002 Physiology
018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 11 Dec 1991
Last Updated on STN: 11 Dec 1991
ED Entered STN: 11 Dec 1991
Last Updated on STN: 11 Dec 1991
AB After coronary occlusion and reflow, carbohydrate catabolism is enhanced, whereas fatty acid utilization is delayed. To test the hypothesis that 'stunning' of fatty acid use by ischemic heart reflects reduced fatty acid transport into the mitochondria, two activities involved in the transport were examined: carnitine-acylcarnitine translocase and carnitine **palmitoyltransferase** II (CPT II). The maximal velocity for carnitine exchange of the translocase is reduced 55% in mitochondria isolated from ischemic canine heart (60-min left circumflex occlusion). Mitochondria from ischemic heart show 50% depletion in total matrix glutathione, a 200% increase in glutathione disulfide (GSSG), and an 80% decrease in the ratio of reduced glutathione (GSH) to GSSG, suggesting that the loss of translocase activity may be a consequence of protein sulfhydryl modifications. In support of this, treatment of these mitochondria with the sulfhydryl-reducing agents, GSH or dithiothreitol, restores carnitine exchange to control. Partial return of mitochondrial GSH and a decrease in GSSG are observed with a 20-min reperfusion of the ischemic myocardium. Continued depression in carnitine exchange with **reperfusion** suggests that other mechanisms may **prevent** restoration of activity. Import of palmitoylcarnitine on the translocase is coupled to palmitoyl-CoA production by CPT II. Mitochondria from ischemic heart with decreased coupling activity also have the lowest palmitoylcarnitine-supported respiratory rates, suggesting that in severely ischemic tissue the translocation-transesterification sequence may become rate limiting to fatty acid oxidation.
CT Medical Descriptors:
*acylcarnitine carnitine translocase
*ischemia
*lipid metabolism
*mitochondrion
dog
controlled study
animal experiment
nonhuman
Drug Descriptors:
*carnitine
*palmitoylcarnitine
RN (carnitine) 461-06-3, 541-15-1, 56-99-5; (palmitoylcarnitine) 1935-18-8, 2364-67-2

ACCESSION NUMBER: 88002764 EMBASE
DOCUMENT NUMBER: 1988002764
TITLE: Effects of chronic admidarone treatment on cat myocardial phospholipid content and on in vitro phospholipid catabolism.
AUTHOR: Shaikh N.A.; Downwar E.
CORPORATE SOURCE: Department of Medicine & Clinical Biochemistry, University of Toronto, Toronto, Ont. M5S 1A8, Canada
SOURCE: Molecular and Cellular Biochemistry, (1987) Vol. 78, No. 1, pp. 17-25. .
ISSN: 0300-8177 CODEN: MCBIB8
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 029 Clinical Biochemistry
037 Drug Literature Index
030 Pharmacology
018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 11 Dec 1991
Last Updated on STN: 11 Dec 1991
ED Entered STN: 11 Dec 1991
Last Updated on STN: 11 Dec 1991
AB Amiodarone is used extensively for the chronic **treatment** of life-threatening arrhythmias caused by **ischemic** heart disease. However, chronic therapy with this agent results in phospholipidosis in various tissues and it has been suggested that the inhibition of lysosomal phospholipase A by this drug contributes to this abnormality. Exogenous amiodarone has been shown to inhibit purified rat liver lysosomal phospholipase A1, as well as acid phospholipase activities of alveolar macrophage homogenates and those of snake venom phospholipase A2 and bacterial phospholipase C. The effects of drug treatment on heart have not been explored. The results described here demonstrate that amiodarone also significantly increases (37%, $p < 0.001$) phospholipid content in cat hearts. This increase is proportionately distributed to all major phospholipid classes, with the exception of **sphingomyelin** which appears to increase more than the others. In addition, the data also showed that following amiodarone treatment, the endogenous drug levels in the heart were sufficient to reduce in vitro losses of membrane phospholipid at 37°C by inhibiting a variety of endogenous phospholipases at physiological (7.4), ischemic (6.2) and acidic (5.0) pH values. This protection is more pronounced at acidic pH values than at physiological pH. Endogenous amiodarone also affects myocardial phospholipase activities towards exogenous phosphatidylcholine and again the extent of inhibition is more at acidic pH. These results suggest that amiodarone induces phospholipidosis in the heart by inhibiting phospholipid catabolism and that its antiarrhythmic properties may reside in its ability to modulate alkaline, neutral and acid phospholipase activities in ischemia. To what extent amiodarone metabolites (desethylamiodarone and bis-desethylamiodarone) are involved in these actions remains to be determined.
CT Medical Descriptors:
*heart
*heart muscle ischemia
cat
animal experiment
animal cell
nonhuman
Drug Descriptors:
*phospholipase

*phospholipase inhibitor
*phospholipid
*amiodarone: PD, pharmacology
RN (phospholipase) 9013-93-8; (amiodarone) 1951-25-3, 19774-82-4, 62067-87-2

L161 ANSWER 111 OF 127 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 86038892 EMBASE
DOCUMENT NUMBER: 1986038892
TITLE: Changed enzyme activities in rat kidney during ischemia.
AUTHOR: Jung K.; Beyer S.
CORPORATE SOURCE: Department of Experimental Organ Transplantation, University Hospital Charite, Humboldt University Berlin, DDR-1017 Berlin, Germany
SOURCE: Journal of Surgical Research, (1985) Vol. 39, No. 5, pp. 454-460. .
CODEN: JSGRA2
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 009 Surgery
028 Urology and Nephrology
029 Clinical Biochemistry
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Dec 1991
Last Updated on STN: 10 Dec 1991
ED Entered STN: 10 Dec 1991
Last Updated on STN: 10 Dec 1991
AB Marker enzyme activities of different subcellular fractions were analyzed in cortex homogenates from rat kidney after different periods (15, 30, 60, and 90 min) of warm ischemia. Lactate dehydrogenase, alanine aminopeptidase, N-acetyl-β-D-glucosaminidase, and succinate-cytochrome c reductase were not altered by ischemia in these periods. ATPase (2,4-dinitrophenol-stimulated and azide-sensitive), 5'-nucleotidase, K-Mg-nitrophenylphosphatase decline within 30 min of ischemia, whereas the microsomal enzymes glucose-6-phosphatase and **NADPH**-cytochrome c **reductase** decreased not before 60 min of ischemia. The early decrease of ATPase and of plasma membrane enzymes can be regarded as a consequence of membrane alterations. This enzymatic approach may be helpful to evaluate **pharmacological** agents for **preventing** and reserving **ischemic** effects in kidneys in a rational manner.
CT Medical Descriptors:
*kidney ischemia
*kidney tubule cell
kidney homogenate
rat
priority journal
animal cell
nonhuman
kidney
Drug Descriptors:
*enzyme
5' nucleotidase
adenosine triphosphatase
n acetyl beta glucosaminidase
glucose 6 phosphatase
lactate dehydrogenase
microsomal aminopeptidase
reduced nicotinamide adenine dinucleotide phosphate ferrihemoprotein reductase

succinate dehydrogenase
RN (5' nucleotidase) 9027-73-0; (adenosine triphosphatase) 37289-25-1, 9000-83-3; (n acetyl beta glucosaminidase) 37278-88-9; (glucose 6 phosphatase) 9001-39-2; (lactate dehydrogenase) 9001-60-9; (microsomal aminopeptidase) 9054-63-1; (reduced nicotinamide adenine dinucleotide phosphate ferrihemoprotein reductase) 9023-03-4; (succinate dehydrogenase) 9002-02-2, 9028-10-8

L161 ANSWER 112 OF 127 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 81026199 EMBASE
DOCUMENT NUMBER: 1981026199
TITLE: [Preoperative **treatment** of electric myocardial **ischemia**].
IL TRATTAMENTO PREOPERATORIO DELL'ISCHEMIA MIOCARDICA ELETTRICA (RICERCHE PERSONALI CON METODO CONTROLLATO).
AUTHOR: Girotto T.; Lorenzin G.; Simini G.
CORPORATE SOURCE: Serv. Anest. Rianim., Osp. Gen. Prov., Este/Padova, Italy
SOURCE: Acta Anaesthesiologica Italica, (1980) Vol. 31, No. 3, pp. 423-432. .
CODEN: AANIBO
COUNTRY: Italy
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
018 Cardiovascular Diseases and Cardiovascular Surgery
024 Anesthesiology
LANGUAGE: Italian
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 9 Dec 1991
Last Updated on STN: 9 Dec 1991
ED Entered STN: 9 Dec 1991
Last Updated on STN: 9 Dec 1991
AB A controlled pharmacological trial was carried out on 350 cases of observed pre-operative myocardial ischaemia. Since most cases of electrical myocardial ischaemia are due to failure of the microvascular-tissue system, results were evaluated on the changes in a lesion number obtained from the features of displacement of the S-T segment in precordial leads. With this trial it was possible to confirm the pathogenetic hypothesis and to suggest the use of experimental drugs alone or in association (fructose-1,6-diphosphate, taurine, CDP-Choline and proxazol) to improve the ischaemic myocardial manifestations in many cases.
CT Medical Descriptors:
*electrocardiography
*heart muscle ischemia
*ischemic heart disease
*preoperative care
*proxazole
ceramide cholinephosphotransferase
clinical study
pathogenesis
drug therapy
heart
etiology
therapy
controlled study
Drug Descriptors:
*citicoline
*fructose bisphosphate
*taurine

RN (citicoline) 56257-85-3, 987-78-0; (taurine) 107-35-7

L161 ANSWER 113 OF 127 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 78277878 EMBASE
DOCUMENT NUMBER: 1978277878
TITLE: **Pharmacological** study for regional **ischemic** infarction of the anterior thalamus in the dog.
AUTHOR: Suzuki J.; Yoshimoto T.; Sakamoto T.
CORPORATE SOURCE: Div. Neurosurg., Inst. Brain Dis., Tohoku Univ. Sch. Med., Sendai, Japan
SOURCE: Acta Medica Nagasakiensia, (1977) Vol. 22, No. 1-2, pp. 22.
.
CODEN: AMNKAB
COUNTRY: Japan
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
008 Neurology and Neurosurgery
030 Pharmacology
020 Gerontology and Geriatrics
LANGUAGE: English

AB The authors discuss the consequences of occluding a cerebral artery in experimental animals which differed significantly in nature, extent and location of pathological changes of the brain. The authors developed a new experimental method in dogs which resulted in a high incidence (more than 70%) of localized ischemic infarction of the anterior thalamus as described elsewhere. This report is concerned with functional alteration of the **ischemic** anterior thalamus after perfusion of the tissue with **pharmacological** solutions. Methods and results: Under Nembutal anesthesia, the internal carotid, posterior communicating, anterior cerebral and middle cerebral artery of a dog were occluded temporarily through a temporal craniotomy. Under electrical monitoring of the ischemic anterior thalamus and the brain cortex, two types of experiments, 20% mannitol perfusion for short term and 7 days administration of CDP-choline, were designed and changes in power spectrum of EEG were compared after the administration with that of a control group of dogs without the treatment. The authors confirmed significant effects of these **pharmacological** solutions on a functional improvement of the **ischemic** tissue by noting a less extensive decrease in fast components of EEGs during occlusion of the arteries and earlier recovery as well after release of the occlusion.

CT Medical Descriptors:
*brain
*brain infarction
***ceramide cholinephosphotransferase**
*dog
*electroencephalography
*infarction
*ischemia
*stroke
*thalamus
central nervous system
animal experiment
cardiovascular system
intravenous drug administration
Drug Descriptors:
*choline
*cytidine diphosphate
*mannitol

RN (choline) 123-41-1, 13232-47-8, 1927-06-6, 4858-96-2, 62-49-7, 67-48-1; (cytidine diphosphate) 63-38-7; (mannitol) 69-65-8, 87-78-5

L161 ANSWER 114 OF 127 PASCAL COPYRIGHT 2006 INIST-CNRS. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 1995-0548453 PASCAL

TITLE (IN ENGLISH): Myocardial and endothelial protection by TMS in ischemia-reperfusion injury

AUTHOR: MUROHARA T.; BUERKE M.; MARGIOTTA J.; RUAN F.; IGARASHI Y.; HAKOMORI S.-I.; LEFER A. M.

CORPORATE SOURCE: Thomas Jefferson univ., Jefferson medical coll., dep. physiology, Philadelphia PA 19107, United States

SOURCE: American journal of physiology. Heart and circulatory physiology, **(1995)**, 38(2), H504-H514, 38 refs.
ISSN: 0363-6135 CODEN: AJPPDI

DOCUMENT TYPE: Journal

BIBLIOGRAPHIC LEVEL: Analytic

COUNTRY: United States

LANGUAGE: English

AVAILABILITY: INIST-670D, 354000054016910130

UP 20001031

AB N,N,N-**trimethylsphingosine** (TMS), a stable synthetic **sphingosine** derivative, was investigated in a feline model of myocardial ischemia (90 min) and reperfusion (270 min) injury. TMS (60 μg/kg), administered intravenously 10 min before reperfusion, significantly attenuated myocardial necrosis (15 ± 3 vs. 31 ± 4% necrosis of area at risk, $P < 0.01$) and cardiac myeloperoxidase activities, a marker of neutrophil accumulation, compared with vehicle-**treated** cats. Endothelium-dependent relaxation to acetylcholine in **ischemic-reperfused** coronary artery rings **treated** with TMS was also significantly preserved compared with vehicle (73 ± 4 vs. 34 ± 4% vasorelaxation, $P < 0.01$). Polymorphonuclear neutrophil (PMN) adherence to coronary endothelium 270 min after **reperfusion** was markedly attenuated in the TMS group compared with vehicle-**treated** cats (37 ± 5 vs. 76 ± 5 PMN/mm.sup.2, $P < 0.01$). TMS also attenuated upregulation of P-selectin on coronary venular endothelium by immunohistochemistry. This was consistent with in vitro findings that TMS attenuates PMN adherence to thrombin-**stimulated** coronary endothelium and P-selectin upregulation on thrombin-**stimulated** cat platelets. A **sphingolipid** derivative, TMS at physiological concentrations exerts cardioprotective actions and preserves coronary endothelial function following myocardial ischemia and reperfusion in vivo. The effects appear to be mediated by the inhibition of PMN-endothelial interaction and subsequent accumulation into the ischemic myocardium. Thus TMS may be a useful agent in attenuating myocardial reperfusion injury.

L161 ANSWER 115 OF 127 LIFESCI COPYRIGHT 2006 CSA on STN

ACCESSION NUMBER: 1999:75167 LIFESCI

TITLE: **Sphingolipids** as Signaling **Modulators** in the Nervous System.

AUTHOR: Ledeen, R.W. [editor]; Hakomori, S.-I. [editor]; Yates, A.J. [editor]; Schneider, J.S. [editor]; Yu, R.K. [editor]

SOURCE: Annals of the New York Academy of Sciences, (**19980619**) 435 pp. The New York Academy of Sciences. US$140.00, hbk..

Meeting Info.: Satellite Symp. to the Combined Meeting of the Int. and Am. Soc. for Neurochem.. New York, NY (USA). **13-16 Jul 1997.**
ISSN: 0077-8923; ,1573311375.
DOCUMENT TYPE: Book
TREATMENT CODE: Conference
FILE SEGMENT: N3
LANGUAGE: English
AB **Sphingolipids** are well-recognized components of virtually all vertebrate and many invertebrate cells, and for many decades were viewed as primarily structural components of cellular membranes. The discovery of potent signaling properties of these substances and their hydrolytic products opened an important new phase of research in **sphingolipids.** Considerable attention was devoted at this conference to the question of neuropathological conditions that were once thought traceable to glycolipids acting as autoantigens. However, a number of reports focused on the phenomenon of molecular mimicry involving glycoprotein components of pathogenic organisms that bear strong structural similarities to certain gangliosides; this was postulated to account for anti-ganglioside antibodies in some patients with Guillain-Barre syndrome and other forms of peripheral neuropathy. As counterpoint to the question of pathology, there was encouraging news regarding potential therapy in accounts of ongoing clinical trials with GM1 ganglioside for **treatment** of Parkinson's disease, **stroke**, and spinal cord injury. Harnessing the neurotrophic properties of gangliosides for neurotherapy has been a long-standing goal of **sphingolipid** researchers, and it is one of the ironies of our period that glycolipids originally isolated from pathological brains are today being considered as potential therapeutic tools.

L161 ANSWER 116 OF 127 LIFESCI COPYRIGHT 2006 CSA on STN
ACCESSION NUMBER: 90:100955 LIFESCI
TITLE: Excitatory amino acids and brain **ischemia**: **Pharmacological** and clinical aspects.
AUTHOR: Biggio, G. [editor]; Spano, P.F. [editor]; Toffano, G. [editor]; Gessa, G.L. [editor]
SOURCE: ADV. BIOSCI., (**1990**) 146 pp. PERMAGON PRESS. ELMSFORD, NY (USA).
ISBN: 0-08-040783-8.
DOCUMENT TYPE: Book
FILE SEGMENT: N3; M
LANGUAGE: English
AB Glutamate lethality following cerebral ischemia is a central theme in volume 78 of Advances in the Biosciences . The volume explores pathophysiological correlates of irreversible ischemic brain damage. The question of free radical involvement in glutamate neurotoxicity is addressed as well as the role of nerve growth factor, the protective **effects** of **sphingolipids** on glutamate-**induced** toxicity, autophagic cell death, and the general paradox of glutamate as an important neurotransmitter. Clinical applications and remedies are also reviewed in this overview of investigation and **treatment** of **ischemic** brain damage.

L161 ANSWER 117 OF 127 BIOENG COPYRIGHT 2006 CSA on STN DUPLICATE 11
ACCESSION NUMBER: 2004340421 BIOENG
DOCUMENT NUMBER: 4033525
TITLES: alpha -Galactosidase A deficient mice: A model of Fabry disease
AUTHOR: Ohshima, T; Murray, GJ; Swaim, WD; Longenecker, G; Quirk, JM; Cardarelli, CO; Sugimoto, Y; Pastan, I; Gottesman,

MM; Brady, RO; Kulkarni, AB*
CORPORATE SOURCE: Bldg. 30, Rm. 132, Natl. Inst. Dent. Res., Natl. Inst. Health, 30 Convent Dr., Bethesda, MD 20892-4326, USA
SOURCE: Proceedings of the National Academy of Sciences, USA [Proc. Natl. Acad. Sci. USA], vol. 94, no. 6, pp. 2540-2544, Mar 1997
ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
SUMMARY LANGUAGE: English
OTHER SOURCE: Genetics Abstracts; Medical and Pharmaceutical Biotechnology Abstracts
UP 20040602
AB Fabry disease is an X-linked inherited metabolic disorder that is **caused** by a deficiency of alpha -galactosidase A (alpha -Gal A). Progressive deposition of neutral **glycosphingolipids** that have terminal alpha -linked galactosyl moieties in vascular endothelial cells **causes** renal failure along with premature myocardial infarctions and **strokes** in patients with this condition. No specific **treatment** is available for patients with this disorder at this time. An animal model of this condition would be valuable for exploring therapeutic strategies for patients with Fabry disease. We report here the generation of alpha -Gal A deficient mice by gene targeting and an analysis of the resulting phenotype. The knockout mice display a complete lack of alpha -Gal A activity. The mice, however, appeared clinically normal at 10 weeks of age. Ultrastructural analysis revealed concentric lamellar inclusions in the kidneys, and confocal microscopy using a fluorescent-labeled lectin specific for alpha -D-galactosyl residues showed accumulation of substrate in the kidneys as well as in cultured fibroblasts. Lipid analysis revealed a marked accumulation of ceramidetrihexoside in the liver and the kidneys. These findings indicate the similarity of the pathophysiological process in the mutant mice and in patients with Fabry disease. The deficiency of alpha -Gal A activity and the accumulation of material containing terminal alpha -galactosyl residues in cultured embryonic fibroblasts derived from alpha -Gal A(-/0) mice were corrected by transducing these cells with bicistronic multidrug resistance retroviruses containing human alpha -Gal A cDNA.

L161 ANSWER 118 OF 127 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2003-01644 BIOTECHDS
TITLE: Inducing blood vessel formation, or **preventing/treating** congestive **heart** failure, **ischemia-reperfusion injury**, **myocardial ischemia** and peripheral arterial diseases in animal, by administering **sphingosine kinase**;
adeno virus or lenti virus vector-mediated gene trasfer and expression in mammal cell for cardiovascular disease gene therapy
AUTHOR: LIAU G; STEFANSSON S; SU J
PATENT ASSIGNEE: NOVARTIS AG; NOVARTIS-ERFINDUNGEN VERW GES MBH
PATENT INFO: WO 2002028406 11 Apr 2002
APPLICATION INFO: WO 2001-EP11513 5 Oct 2001
PRIORITY INFO: US 2000-238230 **5 Oct 2000**; US 2000-238230 5 Oct 2000
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-608171 [65]
AB DERWENT ABSTRACT:
NOVELTY - Inducing blood vessel formation in an animal, or

preventing or **treating** congestive **heart** failure, **myocardial ischemia**, **ischemia-reperfusion injury** and peripheral arterial diseases in an animal, involves administering **sphingosine kinase** (I), its analog, fragment or derivative, to the animal.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) a viral vector (III) including a polynucleotide (II) encoding (I); and (2) expressing (I) in an animal, by administering (II) to the animal.

BIOTECHNOLOGY - Preferred Method: (I) is administered to the animal by administering (II) or an expression vehicle including (II) to the animal. Preferred Vector: The expression vehicle further includes a polynucleotide encoding a protein selected from vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), insulin like growth factor (IGF), angiopoietins, platelet-derived epidermal growth factor (PD-EGF), tumor growth factor-beta (TGF-beta), hypoxia-inducible factor 1 alpha (HIF1-alpha), nitric oxide synthase, monocyte chemoattractant protein-1 (MCP-1), interleukin 8 (IL-8), ephrins, NAP-2 (undefined), ENA-78 (undefined), GROW-alpha (undefined) or active fragments of tyrosyl-tRNA synthetase. (III) is a viral vector, e.g. adenoviral, lentiviral or BIV (bovine immunodeficiency virus).

ACTIVITY - Cardiant; Vasotropic; Vulnerary; Antiulcer.

MECHANISM OF ACTION - Inducer of blood vessel formation (angiogenesis) (claimed). To determine if Av3sphk1alpha induces angiogenesis in vivo, a matrigel implant model in athymic mice was used. S8 cells transduced with Av3sphk1alpha (a viral vector encoding mouse **sphingosine kinase**) at 100 particles per cell were mixed with 0.5 Matrigel and implanted subcutaneously for 7 days. Av3sphk1alpha clearly enhanced bovine fibroblast growth factor (bFGF)-induced angiogenesis as demonstrated by histological analysis. Appearance of larger, mature vessels as well as increased number of CD31-positive vessel structure were apparent in the presence of Av3sphk1alpha transduced cells. By contrast, the control Av3null vector did not enhance angiogenesis.

USE - The method is useful for inducing blood vessel formation in an animal, or **preventing** or **treating** congestive **heart** failure, **myocardial ischemia**, **ischemia-reperfusion injury** and peripheral arterial diseases in an animal, e.g. mammal (such as primate including human) (claimed). (III) is useful for treating diseases or disorders selected from coronary artery disease, peripheral vascular disease, wound healing and fracture repair, reconstructive surgery, transplantation such as islet transplants, tendon repair/sports injury, healing of ulcers, thromboangitis obliterans (Buerger's disease), periodontal tissue regeneration and radiotherapy-induced esophagitis.

ADMINISTRATION - The adenoviral vector is administered at a dose of 107-1012, preferably 5 x 108- 2 x 1011 plaque forming units (pfu). Lentivirus vector is administered at a dose of 5 x 105-1012, preferably 5 x 105-1010 transducing units (claimed). Administration route for the vectors is not given in the specification.

EXAMPLE - Plasmid pCR3.1sphK1alpha, derived from pCR3.1, contained mouse **sphingosine kinase** alpha cDNA. pCR3.1sphK1alpha was digested with HindIII and NotI to isolate a 1531 bp insert containing the coding sequence for sphK1alpha. The fragment was blunt-ended and cloned into EcoRV site of pAVS6alx, an adenoviral shuttle plasmid containing a lox recombination site, to create pAV1xsphK1alpha, pAVS61alx was formed by adding a lox site to pAVS6a. A 535 bp ClaI/NcoI fragment from pAVH8-101 1x, containing the SV40 polyA signal and lox site was inserted into pAVS6a digested with ClaI and NeoI and linearized (4745 bp). The sphK1alpha cDNA was cloned downstream of the RSV promoter, and

the adenoviral tripartite leader sequence, and included the SV40 polyadenylation signal and a homologous recombination region. A large-scale plasmid preparation was prepared using the alkaline lysis method and purified using a CsTFA gradient following standard protocols. The cDNA was then sequenced. The sphK1alpha coding sequence was 1149 kb and encoded a 382 amino acid protein, fully defined in the specification. The sphK1alpha cDNA was incorporated into an adenoviral vector using the lox recombination three-plasmid transfection system. AE1-2a (also called as S8 cells) cells were cultured in Richters media containing 5% heat inactivated fetal bovine serum (FBS). Transient transfections of the AE1-2a cells were performed with the micrograms of NotI-digested pAv1xsphk1alpha, 0.5 micrograms of pCcre and 1 microgram of ClaI-digested pSQ3 DNA using Lipofectamine-PLUS reagent system. Plasmid pSQ3 was a 31574 bp plasmid containing adenoviral structural genes, but was devoid of E1, E2a and E3 sequences. S8 cells were cultured in Lipofectamine reagent/DNA precipitate at 37 degrees Centigrade for 16 hours, and then in Richters media for 5-7 days. A cytopathic effect was observed in cells approximately after 12-15 days post- transfection. The virus was amplified in 15 cm dishes of dexamethasone-induced S8 cells. The recombinant Av3sphk1alpha vector was purified and a large scale seedlot was prepared.(38 pages)

L161 ANSWER 119 OF 127 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2002-13320 BIOTECHDS
TITLE: Identifying compounds that modulate lipid kinase activity, useful for identifying compounds for **treating** e.g. cardiovascular diseases, diabetes, **stroke**, and autoimmune, inflammatory and allergic diseases; recombinant enzyme modulator drug screening
AUTHOR: NORMANT E; MELENDEZ A; CASAMITJANA O; MOREAU F
PATENT ASSIGNEE: WARNER LAMBERT CO
PATENT INFO: WO 2002027318 4 Apr 2002
APPLICATION INFO: WO 2000-EP11250 **29 Sep 2000**
PRIORITY INFO: EP 2000-402684 **29 Sep 2000**
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-383287 [41]
AB DERWENT ABSTRACT:

NOVELTY - Selecting and identifying (M1) compounds that modulate lipid kinase activity comprising: (a) mixing lipid kinase and labeled lipid substrate in the presence of a candidate compound and a source of phosphate; (b) exposing the reaction mixture to a support material which binds the phosphorylated lipid and does not bind unphosphorylated lipid; and(c) assessing the amount of phosphorylated lipid bound to the support, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) a kit for use in M1; and (2) synthesis of a molecule that modulates, inhibits or activates the activity of a lipid kinase comprising carrying out M1, selecting a hit compound exhibiting an inhibitory concentration (IC) 50 value below 10 micro M and using the hit compound in the synthesis of the molecule.

BIOTECHNOLOGY - Preferred Method: The lipid substrate is preferably radiolabeled and is in a micelle. The phosphate source is preferably adenosine triphosphate (ATP). The lipid kinase is a recombinant enzyme, membrane, cytosolic or secreted enzyme. It is preferably **sphingosine kinase** and the substrate is **sphingosine.** The mixture comprises 0.01-10 micro M (preferably 0.01-1 micro M) of unlabeled lipid, 0.01-10 micro Ci (0.01-0.5 micro Ci) of radio-labeled lipid, 0.1-5% (preferably 0.1-1%) detergent such as Triton, phosphatidyl serine, cardiolipine, bovine serum albumin or human

serum albumin, 0.1 micro M-1 mM (0.1-50 micro M) of ATP and the desired amount of total proteins of a cell preparation comprising a lipid kinase. 0-30% of glycerol, preferably 15-25% of glycerol is added to the reaction mixture. Several candidate compounds are tested in parallel. The mixing step is performed in a microtitation plate.

ACTIVITY - Cardiant; antidiabetic; cerebroprotective; immunosuppressive; antiinflammatory; antiallergic; dermatological; antiasthmatic; cytostatic.

MECHANISM OF ACTION - Lipid kinase **modulation**; **sphingosine kinase modulation.** No supporting data is given.

USE - The method is useful for identifying compounds useful for **treating** cardiovascular diseases, diabetes, **stroke**, autoimmune diseases, inflammatory diseases, allergic diseases, dermatitis, T helper-1 related diseases, chronic obstructive pulmonary disease, asthma, cancer and neurodegenerative diseases.

ADVANTAGE - The method provides a simple, reliable, sensitive, convenient and economical process for identifying compounds and can be applied to high throughput equipment.

EXAMPLE - **Sphingosine kinase** was incubated with adenosine triphosphate (ATP), (3H)-**sphingosine** and the test compound in triton micelles for 1 hour. scintillation proximity technology (SPA) beads were added to the wells and the mixture was agitated for 15 minutes and allowed to stand for 1 hour. The plate was then read on a scintillation counter. (44 pages)

L161 ANSWER 120 OF 127 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2002-12183 BIOTECHDS
TITLE: Regulating **angiogenesis** for **treating** cancer and diseases and disorders associated with **angiogenesis**, comprises affecting endothelial differentiation gene-1 receptor-mediated signal transduction; recombinant plasmid vector-mediated gene transfer and expression in host cell, antisense oligonucleotide and antagonist for use in cancer, rheumatoid arthritis, diabetes, Kaposi sarcoma, hemangioma, psoriasis and heartdisease gene therapy
AUTHOR: HLA T; LEE M; CLAFFEY K P; ANCELLIN N; THANGADA S
PATENT ASSIGNEE: UNIV CONNECTICUT
PATENT INFO: WO 2002017899 7 Mar 2002
APPLICATION INFO: WO 2000-US27064 **31 Aug 2000**
PRIORITY INFO: US 2000-651846 **31 Aug 2000**
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-269443 [31]
AB DERWENT ABSTRACT:

NOVELTY - **Regulating** (M1) angiogenesis in vivo, especially **inducing** angiogenesis comprising administering a composition comprising **sphingosine-1-phosphate** (SPP), its analog, (salts or derivatives of SPP or its analogs), or their combination, and inhibiting angiogenesis in vivo, comprising administering an antisense oligonucleotide of an mRNA encoding an endothelial differentiation gene (EDG) protein receptor, is new.

DETAILED DESCRIPTION - **Regulating** (M1) angiogenesis in vivo, especially: (a) **inducing** angiogenesis comprising: (i) administering a composition comprising **sphingosine-1-phosphate** (SPP), its analog, (salts or derivatives of SPP or its analogs), or their combination; or (ii) a gene therapy method comprising constructing and administering pCDNA plasmid vectors expressing one or more of endothelial differentiation gene (EDG)-1, EDG-3 or EDG-5

effective to overexpress one or more of the EDG-1, EDG-3, EDG-5 in the endothelial cells of the body, or adenoviral vectors expressing one or more EDG-1 or EDG-3 effective to overexpress EDG-1 or EDG-3 in the endothelial cells of the body; and (b) inhibiting angiogenesis involves administering an antagonist of EDG-1 signal transduction or an antisense oligonucleotide of an mRNA encoding an EDG protein receptor, is new. INDEPENDENT CLAIMS are also included for the following: (1) promoting (M2) endothelial cell growth and morphogenesis, by treating cells with a bioactive substance that induces signal transduction by a G protein-coupled receptor in endothelial cells; and (2) a composition comprising an antisense oligonucleotide that inhibits in vivo expression of at least one EDG gene.

BIOTECHNOLOGY - Preferred Method: Inducing angiogenesis further comprises administering at least one additional positive angiogenic factor. Angiogenesis is inhibited by administering the antisense oligonucleotide which is a derivative or analog of natural oligonucleotides. The EDG protein receptor is EDG-1, EDG-3 or their combinations. For inhibiting angiogenesis the composition further comprises an additional anti-angiogenic factor, a phosphatidyl inositol (PI)-3-kinase inhibitor, Akt kinase inhibitor, wortmannin, LY294002, or a DNA sequence encoding a mutated EDG-1 receptor, preferably T236A, R231K or R233K. In (M2), the bioactive substance is a lipid such as SPP, its analog, salt, derivative or their combinations.

ACTIVITY - Antirheumatic; Antiarthritic; Antidiabetic; Cytostatic; Antipsoriatic; Antiulcer; Cardiant; Vasotropic; Vulnerary.

MECHANISM OF ACTION - Gene therapy; SPP induces the formation of stress fibers and cortical actin through regulation of the activity of Rho and Rac small guanosine triphosphatase (GTPase), respectively. Regulation of angiogenesis by SPP in vivo was evaluated using a MATRIGEL implant model of subcutaneous angiogenesis in ethylic mice. Female ethylic mice (4-6 weeks old) were injected subcutaneously with 0.4 ml MATRIGEL, premixed with vehicle or fibroblast growth factor-2 (FGF-2) (1.3 microgram/ml) in the absence or presence of various concentrations of SPP. 7 days later, MATRIGEL plugs were harvested along with underlying skin and the gross angiogenic response was recorded. Angiogenesis was quantified by direct counting of vessels containing red blood cells residing in the stroma interface and the MATRIGEL implant. SPP potentiated fibroblast growth factor (FGF)-2-induced angiogenesis in vivo. SPP dramatically enhanced FGF-2 induced angiogenesis, and vascular density and the appearance of mature vascular structures were greatly increased by SPP. Transmission electron microscope analysis indicated that neovessels with well-developed adherens junctions were increased by the FGF-2 and SPP **treatment.** Inhibition of **angiogenesis** by phosphothioate oligonucleotide (PTO: 5'-GACGCTGGTGGGCCCCAT-3') **treatment** was also evaluated. The specificity and efficacy of the PTOs were tested in Xenopus oocytes programmed to express EDG-1 and EDG-3 receptors. Oocytes were injected with 20 ml of capped messenger RNA, premixed with PTO. 32 hours after injections, oocytes were injected with photoprotein aequorin and stimulated with 20 nM of SPP. Light emissions were recorded for 90 seconds with a luminometer. Coinjection of EDG-1 antisense PTO with the EDG-1 cRNA resulted in profound inhibition of EDG-1 expression.

USE - (M1) is useful for regulating (inducing or inhibiting) angiogenesis in vivo. Inducing angiogenesis is useful for protecting endothelial cells from apoptotic cell death, increasing at least one of the VE-cadherin, alpha-catenin, beta-catenin or gamma-catenin at endothelial cell-cell junctions, and modulating vessel maturation. Inhibiting angiogenesis by administering antagonist of signal transduction of EDG-1 or EDG-3 or their combination is useful for treating tumors, rheumatoid arthritis, diabetic retinopathy, Kaposi's

sarcoma, hemangioma or psoriasis, where an additional anti-**angiogenic** factor is also administered, and also for **treating** unwanted **angiogenesis** in a human or animal, where a chicken-anti-human-EDG-1 antibody or its biologically active fragment is also administered with the antagonist of EDG-1 signal transduction. (M2) is useful for promoting vascular or cardiac endothelial cell growth and morphogenesis (all claimed). Inducing angiogenesis is useful to accelerate wound healing in a diabetic ulcers, stomach and other gastrointestinal ulcers, and to induce new vessel growth in myocardium of heart suffering from reduced blood supply due to ischemic heart disease.

ADMINISTRATION - The antisense oligonucleotides are administered by oral, intravenous, intraperitoneal, intramuscular or topical route at a dose of 0.1-100 mg/kg. (79 pages)

L161 ANSWER 121 OF 127 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1997-38112 DRUGU P
TITLE: Amelioration of spatial learning impairment and neuronal loss in rats with stab wounds by prosaposin.
AUTHOR: Hozumi I; Hiraiwa M; Yoneoka U; Inuzaka T; Tsuji S; Akiyama K; Tanaka R; O'Brien J S
CORPORATE SOURCE: Univ.Niigata; Univ.California
LOCATION: Niigata, Jap.; La Jolla, Cal., USA
SOURCE: J.Neurochem. (69, Suppl., S249, 1997)
CODEN: JONRA9 ISSN: 0022-3042
AVAIL. OF DOC.: Department of Neurol., Brain Res. Inst., Univ. Niigata, Niigata 951, Japan.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB **Effects** of prosaposin (PP; the precursors of 4 saposins which activate **sphingolipidhydrolases**, that has been identified as a neurotrophic factor) on spatial learning impairment and neuronal loss were investigated in rats with bilateral stab wounds in the cortices and hippocampi. The wounded rats treated with PP showed significant improvement not only in spatial learning impairment but also in histological examinations. Effectiveness of PP has been reported for brain ischemia previously. This study demonstrated that PP is effective for brain injury. These results raise the possibility that PP may be effective for **preventing** neuronal cell death in neurodegenerative diseases and **brain injury.** (conference abstract).

L161 ANSWER 122 OF 127 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1992-43961 DRUGU P C
TITLE: Semisynthetic Glycosphingolipids in the **Treatment** of Experimental Models of **Stroke.**
AUTHOR: Manev H; Seren M S; Lipartiti H; Lazzaro A; Fadda E; Canella B
CORPORATE SOURCE: Fidia
LOCATION: Abano Terme, Italy
SOURCE: Stroke (23, No. 8, 1200, 1992)
CODEN: SJCCA7 ISSN: 0039-2499
AVAIL. OF DOC.: Fidia Research Laboratories, Abano Terme (PD), Italy.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT; MPC
FILE SEGMENT: Literature
AB Ganglioside derivatives, possessing 'receptor abuse-dependent antagonism'

(RADA) activity were synthesized and tested in models of excitotoxicity and stroke. LIGA4 (GM1 with N-acetyl **sphingosine**), LIGA20 (GM1 with N-dichloroacetylsphyngosine) and PKS3 (d-eritrol, 3-dihydroxy 1-dichloroacetylamide 4-transoctadecene, active metabolite of LIGA20), protected neurons in-vitro from glutamate toxicity. In newborn rat brain, LIGA20 was neuroprotective against NMDA (N-methyl-D-aspartate) toxicity at doses 10 times lower than ganglioside-GM1 (GM1). In an animal model of middle cerebral artery occlusion, LIGA4 caused behavioral improvement and reduced the brain lesion. PK53 was the active metabolite of LIGA20. (congress abstract).

L161 ANSWER 123 OF 127 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1988-05510 DRUGU P B
TITLE: **Prevention** by Amiodarone of Phospholipid Depletion in Isoproterenol-Induced **Ischemia** in Rats.
AUTHOR: Chatelain P; Gremel M; Brotelle R
CORPORATE SOURCE: Sanofi
LOCATION: Brussels, Belgium
SOURCE: Eur.J.Pharmacol. (144, No. 1, 83-90, 1987) 1 Fig. 3 Tab. 35 Ref.
CODEN: EJPHAZ ISSN: 0014-2999
AVAIL. OF DOC.: Sanofi, Centre de Recherche Labaz-Sanofi, 1, av. de Bejar, B-1120, Bruxelles, Belgium.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB In rats, s.c. isoproterenol HCl (IS; Sigma-Chemical) induced ischemia and cardiac hypertrophy due to an edematous and inflammatory reaction, associated with total phospholipids depletion and a decrease in creatine kinase (CK) activity in the myocardium but no change in cholesterol content. Myocardial total phosphatidylcholine (PC), phosphatidylethanolamine (PE), and cardiolipin (CL) levels were reduced and the lysophosphatidylcholine (LC) and lysophosphatidylethanolamine (LE) levels and the LC/PC and LE/PE ratios, FFA and phosphatidic acid levels were increased. I.v. amiodarone HCl (Labaz-Sanofi) or i.p. chlorpromazine HCl (Sigma-Chemical) pretreatment protected against IS-induced phospholipid depletion and the increases in the LC/PC and LE/PE ratios but did not affect IS-induced cardiac hypertrophy and the decrease in CK.

L161 ANSWER 124 OF 127 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1983-36632 DRUGU P B
TITLE: Perturbations of Sarcolemmal and Microsomal Enzymes by Amphiphilic Lipids and Drugs.
AUTHOR: Weglicki W B; Kramer J H; Kennett F F; Knauer T E; Owens K
LOCATION: Oklahoma City, Oklahoma, United States
SOURCE: J.Mol.Cell.Cardiol. (15, Suppl. 1, 291, 1983)
CODEN: JMCDAY ISSN: 0022-2828
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Arachidonyl CoA and propranolol showed synergistic inhibition of sarcolemmal Na+,K+-ATPase in canine cardiocytes. This finding may have clinical relevance for propranolol-**treated** patients who experience elevation of lipid amphiphiles due to **ischemia.** (congress abstract).

L161 ANSWER 125 OF 127 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation

on STN
ACCESSION NUMBER: 1999:332358 SCISEARCH
THE GENUINE ARTICLE: 189UU
TITLE: p38 MAPK inhibition decreases TNF-alpha production and enhances postischemic human myocardial function
AUTHOR: Cain B S (Reprint); Meldrum D R; Meng X Z; Dinarello C A; Shames B D; Banerjee A; Harken A H
CORPORATE SOURCE: Univ Colorado, Hlth Sci Ctr, Dept Surg, C-320, 4200 E 9th Ave, Denver, CO 80262 USA (Reprint); Univ Colorado, Hlth Sci Ctr, Dept Surg, Denver, CO 80262 USA; Univ Colorado, Hlth Sci Ctr, Dept Med, Denver, CO 80262 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF SURGICAL RESEARCH, (**1 MAY 1999**) Vol. 83, No. 1, pp. 7-12.
ISSN: 0022-4804.
PUBLISHER: ACADEMIC PRESS INC, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 52
ENTRY DATE: Entered STN: 1999
Last Updated on STN: 1999
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

ED Entered STN: 1999
Last Updated on STN: 1999

AB Introduction. TNF-alpha is a proinflammatory cytokine implicated in myocardial dysfunction following ischemia/reperfusion (I/R). I/R results in myocardial production of TNF-alpha and TNF-alpha suppresses myocardial contractility, p38 mitogen-activated protein kinase (MAPK) is a redox-sensitive protein kinase involved in intracellular signaling leading to TNF-alpha production. It remains unknown if the human heart produces TNF-alpha after I/R and, if so, whether p38 MAPK is involved.

Hypothesis. p38 MAPK inhibition enhances human myocardial post-IIR contractile function by inhibition of myocardial TNF-alpha production.

Methods. Human atrial trabeculae were suspended in organ baths, field simulated at 1 Hz, and force development was recorded. Following a 90-min equilibration, trabeculae were exposed to a p38 MAPM inhibitor (SB 203580, 1 mu M) or vehicle teach n = 6) prior to simulated ischemia (45 min hypoxia, substrate-free, rapid pacing at 3 Hz) followed by 120 min reoxygenation. Myocardial TNF-alpha levels were measured by ELISA at end reoxygenation.

Results. I/R increased human myocardial TNF-alpha levels from 26.9 +/- 9.3 to 83.9 +/- 19.2 pg/g wet tissue ($P < 0.05$ perfusion vs I/R; ANOVA Bonferroni/Dunn), while p38 MAPK inhibition decreased post-I/R myocardial TNF-alpha levels to 32.3 +/- 8.0 pg/g wet tissue ($P > 0.05$ p38 MAPK inhibition vs I/R). p38 MAPK inhibition improved postischemic force development from 18.5 +/- 2.1 to 37.0 +/- 2.0% baseline developed force (%BDF; $P < 0.05$ I/R vs p38 MAPK inhibition).

Conclusions. (1) The human heart produces TNF-alpha after I/R, (2) p38 MAPK mediates myocardial I/R- induced TNF-alpha production, (3) p38 MAPK inhibition limits functional impairment after I/R, and (4) inhibition of **ischemia**-induced TNF-alpha production may represent a potent **therapeutic** strategy for improving myocardial function after angioplasty, coronary bypass, or heart transplantation. (C) 1999 Academic Press.

L161 ANSWER 126 OF 127 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1998:160148 SCISEARCH
THE GENUINE ARTICLE: YY248

TITLE: Increased myocardial tumor necrosis factor-alpha in a crystalloid-perfused model of cardiac ischemia-reperfusion injury
AUTHOR: Meldrum D R (Reprint); Cleveland J C; Cain B S; Meng X Z; Harken A H
CORPORATE SOURCE: Univ Colorado, Hlth Sci Ctr, Div Cardiothorac Surg, Dept Surg, 4200 E 9th Ave, Box C-306, Denver, CO 80262 USA (Reprint); Univ Colorado, Hlth Sci Ctr, Div Cardiothorac Surg, Dept Surg, Denver, CO 80262 USA
COUNTRY OF AUTHOR: USA
SOURCE: ANNALS OF THORACIC SURGERY, (**FEB 1998**) Vol. 65, No. 2, pp. 439-443.
ISSN: 0003-4975.
PUBLISHER: ELSEVIER SCIENCE INC, 655 AVENUE OF THE AMERICAS, NEW YORK, NY 10010 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 31
ENTRY DATE: Entered STN: 1998
Last Updated on STN: 1998
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

ED Entered STN: 1998
Last Updated on STN: 1998

AB Background. The heart is a tumor necrosis factor-alpha (TNF-alpha)-producing organ. Recent basic experimental and clinical evidence suggests that TNF-alpha is an important mediator of myocardial injury during acute myocardial infarction, chronic heart failure, cardiac allograft rejection, and cardiopulmonary bypass operations. Although it is known that the myocardium itself is capable of producing TNF-alpha in response to endotoxin, it is unknown whether there is an increase in myocardial tissue TNF-alpha levels after ischemia-reperfusion injury. We hypothesized that ischemia-reperfusion induces the production of TNF-alpha by the heart.

Methods. To avoid blood-borne TNF-alpha as a potentially confounding variable, we examined myocardial TNF-alpha production in a crystalloid-perfused model of cardiac ischemia-reperfusion injury. Isolated rat hearts were perfused with crystalloid solution and subjected to ischemia-reperfusion. Postischemic myocardial TNF-alpha was measured using an enzyme-linked immunosorbent assay and correlated with developed pressure, coronary flow, end-diastolic pressure, and creatine kinase loss (assay of activity in coronary effluent).

Results. Ischemia-reperfusion induced a marked increase in myocardial TNF-alpha that was associated with decreased myocardial contractility and coronary flow and with increased end-diastolic pressure and postischemic creatine kinase loss.

Conclusions. The heart produces TNF-alpha in response to ischemia-reperfusion. Ischemia-induced TNF-alpha production may contribute to postischemic myocardial stunning, necrosis, or both. Strategies designed to limit **ischemia**-induced myocardial TNF-alpha production may have **therapeutic** utility in the settings of planned myocardial **ischemic** events. (C) 1998 by The Society of Thoracic Surgeons.

L161 ANSWER 127 OF 127 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1995:549097 SCISEARCH
THE GENUINE ARTICLE: RP467
TITLE: MYOCARDIAL AND ENDOTHELIAL PROTECTION BY TMS IN ISCHEMIA-REPERFUSION INJURY
AUTHOR: MUROHARA T (Reprint); BUERKE M; MARGIOTTA J; RUAN F Q;

IGARASHI Y; HAKOMORI S I; LEFER A M
CORPORATE SOURCE: THOMAS JEFFERSON UNIV, JEFFERSON MED COLL, DEPT PHYSIOL, PHILADELPHIA, PA 19107 USA; BIOMEMBRANE INST, SEATTLE, WA 98119 USA; UNIV WASHINGTON, DEPT PATHOBIOL, SEATTLE, WA 98195 USA
COUNTRY OF AUTHOR: USA
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY-HEART AND CIRCULATORY PHYSIOLOGY, (**AUG 1995**) Vol. 38, No. 2, pp. H504-H514.
ISSN: 0363-6135.
PUBLISHER: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 38
ENTRY DATE: Entered STN: 1995
Last Updated on STN: 1995
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

ED Entered STN: 1995
Last Updated on STN: 1995

AB N,N,N-**trimethylsphingosine** (TMS), a stable synthetic **sphingosine** derivative, was investigated in a feline model of myocardial ischemia (90 min) and reperfusion (270 min) injury. TMS (60 mu g/kg), administered intravenously 10 min before reperfusion, significantly attenuated myocardial necrosis (15 +/- 3 vs. 31 +/- 4% necrosis of area at risk, P < 0.01) and cardiac myeloperoxidase activities, a marker of neutrophil accumulation, compared with vehicle-treated cats. Endothelium-dependent relaxation to acetylcholine in **ischemic-reperfused** coronary artery rings **treated** with TMS was also significantly preserved compared with vehicle (73 +/- 4 vs. 34 +/- 4% vasorelaxation, P < 0.01). Polymorphonuclear neutrophil (PMN) adherence to coronary endothelium 270 min after **reperfusion** was markedly attenuated in the TMS group compared with vehicle-**treated** cats (37 +/- 5 vs. 76 +/- 5 PMN/mm(2), P < 0.01). TMS also attenuated upregulation of P-selectin on coronary venular endothelium by immunohistochemistry. This was consistent with in vitro findings that TMS attenuates PMN adherence to thrombin-stimulated coronary endothelium and P-selectin upregulation on thrombin-stimulated cat platelets. A **sphingolipid** derivative, TMS at physiological concentrations exerts cardioprotective actions and preserves coronary endothelial function following myocardial ischemia and reperfusion in vivo. The effects appear to be mediated by the inhibition of PMN-endothelial interaction and subsequent accumulation into the ischemic myocardium. Thus TMS may be a useful agent in attenuating myocardial reperfusion injury.

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=> d que 144
L5              QUE  ABB=ON  PLU=ON  SABBADINI, R?/AU
L9              QUE  ABB=ON  PLU=ON  ?ENZYM?
L10             QUE  ABB=ON  PLU=ON  ?SPHINGO? OR ?CERAMID? OR KETOSPHING
                ? OR GALACTOSYLCERAMID? OR DIHYDROCERAMID?
L11             QUE  ABB=ON  PLU=ON  CEREBROSID? OR ?PALMITOYLTRANSFER? O
                R (?PALMITOYL?(1A)TRANSFERAS?) OR (NADPH(3A)REDUCTAS?)
L12             QUE  ABB=ON  PLU=ON  HEART? OR ?CORONAR? OR ?CARDIO? OR ?
                CARDIA? OR MYOCARD?
L13             QUE  ABB=ON  PLU=ON  ISCHEM? OR POSTISCHEM? OR REPERFUS?
                OR NEOVASCUL? OR (NEO(W)VASCUL?) OR ANGIOGEN? OR (ANGIO(W
                )GENE?) OR STENT? OR ?STENOSIS? OR RESTENOSIS? OR STROKE?
L14             QUE  ABB=ON  PLU=ON  ?CEREBR? OR BRAIN
L15             QUE  ABB=ON  PLU=ON  VASCU? OR VEIN? OR ARTER?
L19             QUE  ABB=ON  PLU=ON  SURGERY+PFT,OLD,NT/CT
L20             QUE  ABB=ON  PLU=ON  ISCHEMIA+PFT,OLD,NT/CT
L21             QUE  ABB=ON  PLU=ON  STROKE+PFT,OLD,NT/CT
L22             QUE  ABB=ON  PLU=ON  "HEART, DISEASE"+PFT,OLD,NT/CT
L23             QUE  ABB=ON  PLU=ON  REPERFUSION+PFT,OLD,NT/CT
L24             QUE  ABB=ON  PLU=ON  "BRAIN, DISEASE"+PFT,OLD,NT/CT
L25             QUE  ABB=ON  PLU=ON  ANGIOGENESIS+PFT,OLD,NT/CT
L26             QUE  ABB=ON  PLU=ON  "CARDIOVASCULAR SYSTEM, DISEASE"+PFT
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L27             QUE  ABB=ON  PLU=ON  CERAMIDES+PFT,OLD,NT/CT
L28             QUE  ABB=ON  PLU=ON  SPHINGOMYELINS+PFT,OLD,NT/CT
L29             QUE  ABB=ON  PLU=ON  "ENZYMES, BIOLOGICAL STUDIES"+PFT,OL
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L30             QUE  ABB=ON  PLU=ON  ENZYMES+PFT,OLD/CT
L31             QUE  ABB=ON  PLU=ON  SPHINGOLIPIDS+PFT,OLD,NT/CT
L32             QUE  ABB=ON  PLU=ON  SPHINGOSINES+PFT,OLD,NT/CT
L36          20 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5 AND (L10 OR (L27 OR L28)
                OR (L31 OR L32) OR L11)
L37          15 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L36 AND ((L12 OR L13 OR L14
                OR L15) OR (L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR
                L26))
L38             QUE  ABB=ON  PLU=ON  ENZYM?/CW
L39           2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L37 AND ((L29 OR L30) OR L38
                OR L9)
L41             QUE  ABB=ON  PLU=ON  ?SPHINGO?
L42          15 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L37 AND L41
L43          10 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L42 AND (?SPHINGO?/CW)
L44          10 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L39 OR L43


=> d que 185
L5              QUE  ABB=ON  PLU=ON  SABBADINI, R?/AU
L85           4 SEA FILE=WPIX ABB=ON  PLU=ON  L5 AND ?SPHINGO?/BIX


=> d que 1100
L5              QUE  ABB=ON  PLU=ON  SABBADINI, R?/AU
L12             QUE  ABB=ON  PLU=ON  HEART? OR ?CORONAR? OR ?CARDIO? OR ?
                CARDIA? OR MYOCARD?
L13             QUE  ABB=ON  PLU=ON  ISCHEM? OR POSTISCHEM? OR REPERFUS?
                OR NEOVASCUL? OR (NEO(W)VASCUL?) OR ANGIOGEN? OR (ANGIO(W
                )GENE?) OR STENT? OR ?STENOSIS? OR RESTENOSIS? OR STROKE?
L14             QUE  ABB=ON  PLU=ON  ?CEREBR? OR BRAIN
L15             QUE  ABB=ON  PLU=ON  VASCU? OR VEIN? OR ARTER?
L70             QUE  ABB=ON  PLU=ON  TREAT? OR ?THERAP? OR MEDIC? OR PHAR
                M?
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L71             QUE  ABB=ON  PLU=ON  PREVENT? OR AVOID?
L72             QUE  ABB=ON  PLU=ON  ADMIN?
L98          19 SEA FILE=MEDLINE ABB=ON  PLU=ON  L5 AND ?SPHINGO?
L99          14 SEA FILE=MEDLINE ABB=ON  PLU=ON  L98 AND (L12 OR L13 OR L14 OR
                L15)
L100         11 SEA FILE=MEDLINE ABB=ON  PLU=ON  L99 AND (L70 OR L71 OR L72)


=> d que l123
L5              QUE  ABB=ON  PLU=ON  SABBADINI, R?/AU
L12             QUE  ABB=ON  PLU=ON  HEART? OR ?CORONAR? OR ?CARDIO? OR ?
                CARDIA? OR MYOCARD?
L13             QUE  ABB=ON  PLU=ON  ISCHEM? OR POSTISCHEM? OR REPERFUS?
                OR NEOVASCUL? OR (NEO(W)VASCUL?) OR ANGIOGEN? OR (ANGIO(W
                )GENE?) OR STENT? OR ?STENOSIS? OR RESTENOSIS? OR STROKE?
L14             QUE  ABB=ON  PLU=ON  ?CEREBR? OR BRAIN
L15             QUE  ABB=ON  PLU=ON  VASCU? OR VEIN? OR ARTER?
L70             QUE  ABB=ON  PLU=ON  TREAT? OR ?THERAP? OR MEDIC? OR PHAR
                M?
L71             QUE  ABB=ON  PLU=ON  PREVENT? OR AVOID?
L72             QUE  ABB=ON  PLU=ON  ADMIN?
L79             QUE  ABB=ON  PLU=ON  SMASE
L80             QUE  ABB=ON  PLU=ON  SPHINGOMYELINAS?
L121         19 SEA FILE=EMBASE ABB=ON  PLU=ON  L5 AND (?SPHINGO? OR L79 OR
                L80)
L122         15 SEA FILE=EMBASE ABB=ON  PLU=ON  L121 AND (L12 OR L13 OR L14 OR
                L15)
L123          9 SEA FILE=EMBASE ABB=ON  PLU=ON  L122 AND (L70 OR L71 OR L72)


=> d his l160

     (FILE 'BIOSIS, PASCAL, JICST-EPLUS, CABA, LIFESCI, BIOENG, BIOTECHNO,
     BIOTECHDS, DRUGU, DRUGB, VETU, VETB, SCISEARCH, CONFSCI, DISSABS' ENTERED
     AT 13:22:58 ON 11 JUL 2006)
L160         11 S L159 AND L70-L72

=> d que l160
L5              QUE  ABB=ON  PLU=ON  SABBADINI, R?/AU
L14             QUE  ABB=ON  PLU=ON  ?CEREBR? OR BRAIN
L15             QUE  ABB=ON  PLU=ON  VASCU? OR VEIN? OR ARTER?
L41             QUE  ABB=ON  PLU=ON  ?SPHINGO?
L70             QUE  ABB=ON  PLU=ON  TREAT? OR ?THERAP? OR MEDIC? OR PHAR
                M?
L71             QUE  ABB=ON  PLU=ON  PREVENT? OR AVOID?
L72             QUE  ABB=ON  PLU=ON  ADMIN?
L79             QUE  ABB=ON  PLU=ON  SMASE
L80             QUE  ABB=ON  PLU=ON  SPHINGOMYELINAS?
L132            QUE  ABB=ON  PLU=ON  ?ISCHAEM?
L158        100 SEA L5 AND (L41 OR L79 OR L80)
L159         19 SEA L158 AND (LL12 OR L132 OR L14 OR L15)
L160         11 SEA L159 AND (L70 OR L71 OR L72)


=> dup rem l44 l85 l100 l123 l160
FILE 'HCAPLUS' ENTERED AT 13:52:31 ON 11 JUL 2006
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PROCESSING COMPLETED FOR L44
PROCESSING COMPLETED FOR L85
PROCESSING COMPLETED FOR L100
PROCESSING COMPLETED FOR L123
PROCESSING COMPLETED FOR L160
L162 23 DUP REM L44 L85 L100 L123 L160 (22 DUPLICATES REMOVED)
ANSWERS '1-10' FROM FILE HCAPLUS
ANSWERS '11-12' FROM FILE WPIX
ANSWERS '13-17' FROM FILE MEDLINE
ANSWER '18' FROM FILE EMBASE
ANSWERS '19-23' FROM FILE BIOSIS

=> file stnguide
FILE 'STNGUIDE' ENTERED AT 13:53:05 ON 11 JUL 2006
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AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jul 7, 2006 (20060707/UP).

=> d ibib ed ab 1-23
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS' -
CONTINUE? (Y)/N:y

L162 ANSWER 1 OF 23 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2003:236448 HCAPLUS
DOCUMENT NUMBER: 139:378528
TITLE: Factor Associated With Neutral **Sphingomyelinase** Activation and Its Role in **Cardiac** Cell Death
AUTHOR(S): O'Brien, Nicole W.; Gellings, Nicole M.; Guo, Mei; Barlow, Steven B.; Glembotski, Christopher C.; **Sabbadini, Roger A.**
CORPORATE SOURCE: SDSU Heart Institute and Department of Biology, San Diego State University, San Diego, CA, USA
SOURCE: Circulation Research (2003), 92(6), 589-591
CODEN: CIRUAL; ISSN: 0009-7330
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 27 Mar 2003

AB Generation of proapoptotic **sphingolipids** by neutral **sphingomyelinase** activation is an early response to hypoxia/reoxygenation (HR) in **cardiomyocytes.** Factor associated with neutral **sphingomyelinase** activation (FAN) mediates activation of **sphingomyelinase** and subsequent apoptosis. However, the participation of FAN in HR-induced **cardiomyocyte** cell death has not been elucidated. We therefore investigated the expression and role of FAN in rat **cardiomyocytes.** A cDNA was isolated from rat **heart** encoding putative rat FAN. Reverse transcriptase-polymerase chain reaction, immunoelectron microscopy, and immunofluorescence demonstrated for the first time the expression of FAN specifically in rat **cardiomyocytes.** FAN expression was confirmed by the finding that expression of a dominant-neg. FAN almost completely abrogated HR-induced cell death, whereas overexpression of wild-type FAN led to an increase. Treatment of FAN and dominant-neg. FAN-expressing cells with C2-**ceramide** produced substantial cell death, indicating dominant-neg. FAN exerts its protective action by interfering with the activation of the **sphingolipid** cascade. Taking these results together, we conclude that FAN is a previously undescribed and important HR signaling component in the **heart** and that inhibition of FAN may provide a novel intervention point for reducing **ischemia/reperfusion** injury.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L162 ANSWER 2 OF 23 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2003:519095 HCAPLUS
DOCUMENT NUMBER: 139:259165
TITLE: Predicting obstructive **coronary artery** disease with serum **sphingosine** -1-phosphate
AUTHOR(S): Deutschman, Douglas H.; Carstens, Jeffrey S.; Klepper, Robert L.; Smith, Wyatt S.; Page, M. Trevor; Young, Thomas R.; Gleason, Lisa A.; Nakajima, Nobuko; **Sabbadini, Roger A.**
CORPORATE SOURCE: SDSU Heart Institute and Department of Biology, San Diego State University, San Diego, CA, 92182, USA
SOURCE: American Heart Journal (2003), 146(1), 62-68
CODEN: AHJOA2; ISSN: 0002-8703
PUBLISHER: Mosby, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 08 Jul 2003
AB Background: **Sphingolipids** are emerging as important signaling mols. that may be produced by **cardiac** tissue during **ischemic** stress or as a consequence of inflammation. Because both inflammation and **myocardial ischemia** are associated with **coronary artery** disease (CAD), a study was designed to test the ability of serum **sphingolipids** to predict obstructive CAD. Methods: The study consisted of 308 consecutive patients undergoing **coronary** angiog. for all indications. The primary data points were the assessment of **coronary artery stenosis** with angiog. and the measurements of serum **sphingolipids.** Results: In this diverse population, serum **sphingosine**-1-phosphate (S1P) was a significant predictor of CAD ($P < .001$). Multivariate anal. with logistic regression demonstrated that serum S1P was more predictive of obstructive CAD (odds ratio = 7.61) than the traditional risk factors (age, sex, family history of CAD, diabetes mellitus, lipid profile, hypertension, etc.). A 3-variable S1PC composite score was derived by combining the power of the S1P marker with the 2 most

important risk factors, age and sex. The relationship between the S1PC and CAD scores was continuous and progressive, such that patients with elevated S1PC scores had higher occurrences of obstructive CAD. S1PC was also predictive of disease severity; 53.2% of patients in the fourth S1PC quartile had 2 to 3 vessel CAD, whereas only 5.2% of patients in the first S1PC quartile had 2 to 3 vessel disease (RR = 10.2 for severity). Conclusions: Serum S1P is a remarkably strong and robust predictor of both the occurrence and severity of **coronary stenosis.** An S1P-based composite score may be useful as a novel, non-invasive indicator of obstructive CAD.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L162 ANSWER 3 OF 23 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 2002:504646 HCAPLUS
DOCUMENT NUMBER: 137:83610
TITLE: Compositions and methods for the treatment and prevention of **cardiovascular** diseases and disorders, and for identifying agents therapeutic therefor
INVENTOR(S): **Sabbadini, Roger A.**
PATENT ASSIGNEE(S): Medlyte, Inc., USA
SOURCE: PCT Int. Appl., 188 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2002051439	A2	20020704	WO 2001-US50785		20011221
WO 2002051439	A3	20030814			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2432978	AA	20020704	CA 2001-2432978		20011221
US 2003026799	A1	20030206	US 2001-28156		20011221
US 6881546	B2	20050419			
US 2003027304	A1	20030206	US 2001-29401		20011221
US 6858383	B2	20050222			
US 2003096022	A1	20030522	US 2001-29372		20011221
EP 1363643	A2	20031126	EP 2001-987517		20011221
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
US 2004247603	A1	20041209	US 2004-820582		20040407
US 2005226862	A1	20051013	US 2005-101976		20050407
PRIORITY APPLN. INFO.:			US 2000-257926P	P	20001222
			US 2001-28156	A3	20011221
			WO 2001-US50785	W	20011221

OTHER SOURCE(S): MARPAT 137:83610
ED Entered STN: 05 Jul 2002
AB Methods and compns. are disclosed that are useful for the prevention

and/or treatment of **cardiovascular** and **cardiac** diseases and disorders, or damage resulting from surgical or medical procedures that may cause **ischemic** or **ischemic/reperfusion** damage in humans; and **cardiovascular** trauma. The beneficial effects of the compns. and methods are achieved through the use of pharmaceutical compns. that include agents that interfere with the production and/or biol. activities of **sphingolipids** and their metabolites, particularly **sphingosine** (SPH) and **sphingosine**-1-phosphate (S-1-P). Also disclosed are methods for identifying and isolating therapeutic agents.

L162 ANSWER 4 OF 23 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 1999:8212 HCAPLUS
DOCUMENT NUMBER: 130:63348
TITLE: Methods, kits, devices, and compositions for early detection of **heart** disease by measuring level of **sphingolipid**
INVENTOR(S): **Sabbadini, Roger A.**
PATENT ASSIGNEE(S): Medlyte Diagnostics, Inc., USA
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9857179	A1	19981217	WO 1998-US10486	19980522
W: AU, CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2293718	AA	19981217	CA 1998-2293718	19980522
AU 9875901	A1	19981230	AU 1998-75901	19980522
EP 988552	A1	20000329	EP 1998-923666	19980522
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6210976	B1	20010403	US 1998-84069	19980522
JP 2002504999	T2	20020212	JP 1999-502510	19980522
US 6534322	B1	20030318	US 2000-489158	20000121
US 6534323	B1	20030318	US 2000-489466	20000121
AU 2002035620	A5	20020613	AU 2002-35620	20020424
AU 781271	B2	20050512		
AU 2005201211	A1	20050414	AU 2005-201211	20050321

PRIORITY APPLN. INFO.:		
US 1997-49274P	P	19970610
US 1998-84069	A3	19980522
WO 1998-US10486	W	19980522
AU 2002-35620	A3	20020424

ED Entered STN: 06 Jan 1999
AB The invention relates to methods, compns., kits, and devices for detecting **cardiac ischemia**, hypoxia, or other causes of **heart** failure in a mammal by obtaining a test sample from a mammal, measuring a level of a non-polypeptidic **cardiac** marker (e.g. **sphingolipid**) in the test sample, and determining if the level of the **cardiac** marker measured in the test sample correlates with **cardiac ischemia** or hypoxia or another form of **heart** failure. Serum **sphingosine** levels were determined by HPLC. The level in **ischemic** patients was about 7-fold higher than the age-matched control group and about 160-fold higher than well-conditioned military personnel and athletes undergoing severe

exercise stress.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L162 ANSWER 5 OF 23 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 1997:176906 HCAPLUS
DOCUMENT NUMBER: 126:260481
TITLE: **Sphingosylphosphocholine** modulates the ryanodine receptor/calcium-release channel of **cardiac** sarcoplasmic reticulum membranes
AUTHOR(S): Betto, Romeo; Teresi, Alessandra; Turcato, Federica; Salviati, Giovanni; **Sabbadini, Roger A.**; Krown, Kevin; Glembotski, Chris C.; Kindman, L. Allen; Dettbarn, Christine; et al.
CORPORATE SOURCE: C. N. R. Unit for Muscle Biology and Physiopathology, c/o Department of Biomedical and Experimental Sciences, University of Padova, Padua, 35121, Italy
SOURCE: Biochemical Journal (1997), 322(1), 327-333
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 15 Mar 1997
AB **Sphingosylphosphocholine** (SPC) modulates Ca2+ release from isolated **cardiac** sarcoplasmic reticulum membranes; 50 μM SPC induces the release of 70-80% of the accumulated calcium. SPC releases calcium from **cardiac** sarcoplasmic reticulum through the ryanodine receptor, since the release is inhibited by the ryanodine receptor channel antagonists ryanodine, Ruthenium Red and **sphingosine.** In intact **cardiac** myocytes, even in the absence of extracellular calcium, SPC causes a rise in diastolic Ca2+, which is greatly reduced when the sarcoplasmic reticulum is depleted of Ca2+ by prior thapsigargin treatment. SPC action on the ryanodine receptor is Ca2+-dependent. SPC shifts to the left the Ca2+-dependence of [3H]ryanodine binding, but only at high pCa values, suggesting that SPC might increase the sensitivity to calcium of the Ca2+-induced Ca2+-release mechanism. At high calcium concns. (pCa 4.0 or lower), where [3H]ryanodine binding is maximally stimulated, no effect of SPC is observed We conclude that SPC releases calcium from **cardiac** sarcoplasmic reticulum membranes by activating the ryanodine receptor and possibly another intracellular Ca2+-release channel, the **sphingolipid** Ca2+-release-mediating protein of endoplasmic reticulum (SCaMPER) [Mao, Kim, Almenoff, Rudner, Kearney and Kindman (1996) Proc. Natl. Acad. Sci. U.S.A 93, 1993-1996], which we have identified for the first time in **cardiac** tissue.

L162 ANSWER 6 OF 23 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 8
ACCESSION NUMBER: 1997:3063 HCAPLUS
DOCUMENT NUMBER: 126:46107
TITLE: Tumor necrosis factor alpha-induced apoptosis in **cardiac** myocytes. Involvement of the **sphingolipid** signaling cascade in **cardiac** cell death
AUTHOR(S): Krown, Kevin A.; Page, M. Trevor; Nguyen, Cuong; Zechner, Dietmar; Gutierrez, Veronica; Comstock, Kevyn L.; Glembotski, Christopher C.; Quintana, Penelope J. E.; **Sabbadini, Roger A.**
CORPORATE SOURCE: Dep. Biol., San Diego State Univ., San Diego, CA, 92182, USA
SOURCE: Journal of Clinical Investigation (1996), 98(12),

2854-2865
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 04 Jan 1997
AB It was shown here that physiol. relevant levels of the proinflammatory cytokine TNFα induced apoptosis in rat **cardiomyocytes** in vitro, as quantified by single cell microgel electrophoresis of nuclei (" **cardiac** comets") as well as by morphol. and biochem. criteria. It was also shown that TNFα stimulated production of the endogenous second messenger, **sphingosine**, suggesting **sphingolipid** involvement in TNFα-mediated **cardiomyocyte** apoptosis. Consistent with this hypothesis, **sphingosine** strongly induced **cardiomyocyte** apoptosis. The ability of the appropriate stimulus to drive **cardiomyocytes** into apoptosis indicated that these cells were primed for apoptosis and were susceptible to clin. relevant apoptotic triggers, such as TNFα. Apparently the elevated TNFα levels seen in a variety of clin. conditions, including sepsis and **ischemic myocardial** disorders, may contribute to TNFα-induced **cardiac** cell death. **Cardiomyocyte** apoptosis is also discussed in terms of its potential beneficial role in limiting the area of **cardiac** cell involvement as a consequence of **myocardial** infarction, viral infection, and primary **cardiac** tumors.

L162 ANSWER 7 OF 23 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 9
ACCESSION NUMBER: 1995:300458 HCAPLUS
DOCUMENT NUMBER: 122:75083
TITLE: Involvement of ryanodine receptors in **sphingosylphosphorylcholine**-induced calcium release from **brain** microsomes
AUTHOR(S): Dettbarn, Christine; Betto, Romeo; Salviati, Giovanni; **Sabbadini, Roger**; Palade, Philip
CORPORATE SOURCE: Department of Physiology and Biophysics, University of Texas Medical Branch, Galveston, TX, 77555-0641, USA
SOURCE: Brain Research (1995), 669(1), 79-85
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 19 Jan 1995
AB **Sphingosylphosphorylcholine** (SPC) releases Ca2+ from **brain** microsomes. SPC-induced Ca2+ release differs from IP3-induced Ca2+ release in that it is more extensive in the **cerebrum** than in the cerebellum. SPC has little effect on [3H] IP3 binding but enhances [3H] ryanodine binding, as expected for an activator of ryanodine receptors. SPC-induced Ca2+ release is inhibited by ryanodine receptor blockers but not by selective blockers of IP3 receptors. The authors conclude that SPC releases Ca2+ from **brain** microsomes by activating ryanodine receptors rather than IP3 receptors. Activation of an addnl. SPC-sensitive pathway for releasing Ca2+ is not precluded.

L162 ANSWER 8 OF 23 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 11
ACCESSION NUMBER: 1995:230062 HCAPLUS
DOCUMENT NUMBER: 122:52618
TITLE: Control of **cardiac** Ca2+ levels. Inhibitory actions of **sphingosine** on Ca2+ transients and L-type Ca2+ channel conductance

AUTHOR(S): McDonough, Patrick M.; Yasui, Kenji; Betto, Romeo; Salviati, Giovanni; Glembotski, Christopher C.; Palade, Philip T.; **Sabbadini, Roger A.**
CORPORATE SOURCE: Department of Biology, San Diego State Univ., San Diego, CA, 92182, USA
SOURCE: Circulation Research (1994), 75(6), 981-9
CODEN: CIRUAL; ISSN: 0009-7330
PUBLISHER: American Heart Association
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 07 Dec 1994
AB The naturally occurring second messenger **sphingosine** (SPH) was examined for its ability to influence **cardiac** myocyte Ca2+ regulation. SPH inhibited intracellular Ca2+ transients in adult and neonatal rat ventricular myocytes. The inhibition was steeply dose dependent, with complete blockage of the Ca2+ transients occurring in the 20- to 25-μmol/L range. Whole-cell patch clamping revealed substantial inhibition of the L-type Ca2+ channel current (ICa) by SPH. The ability of SPH to block both the Ca2+ transients and ICa was not dependent on protein kinases, since the general protein kinase inhibitor H7 failed to prevent the actions of SPH. The specificity of the effect of SPH was determined in expts. showing that SPH analogs did not produce comparable effects. Neither the naturally occurring **ceramide**, N-stearoyl-SPH, nor the cell-permeant **ceramide**, N-acetyl-SPH, had SPH-like actions on the Ca2+ transients or L-type channel conductances. Caffeine-induced Ca2+ transients were also inhibited by the actions of SPH on **cardiac** sarcoplasmic reticulum Ca2+ release, and the threshold for caffeine-induced Ca2+ release was raised. The authors conclude that SPH inhibits excitation-contraction coupling in **cardiac** myocytes by reducing the amount of entering "trigger Ca2+" for Ca2+-induced Ca2+ release and by simultaneously raising the threshold of the ryanodine receptor for Ca2+-induced Ca2+ release. Consequently, the authors propose that **sphingolipids** produced by the **sphingomyelin** signal transduction pathway could be physiol. relevant regulators of **cardiac** [Ca2+]i and therefore **cardiac** contractility.

L162 ANSWER 9 OF 23 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 12
ACCESSION NUMBER: 1994:241230 HCAPLUS
DOCUMENT NUMBER: 120:241230
TITLE: Modulation of **cardiac** sarcoplasmic reticulum ryanodine receptor by **sphingosine**
AUTHOR(S): Dettbarn, Christine A.; Betto, Romeo; Salviati, Giovanni; Palade, Philip; Jenkins, Gary M.; **Sabbadini, Roger A.**
CORPORATE SOURCE: Med. Branch, Univ. Texas, Galveston, TX, 77550, USA
SOURCE: Journal of Molecular and Cellular Cardiology (1994), 26(2), 229-42
CODEN: JMCDAY; ISSN: 0022-2828
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 14 May 1994
AB Excitation contraction (EC) coupling in muscle cells involves the movement of calcium through the calcium-release channel of the sarcoplasmic reticulum (SR) membrane known as the ryanodine receptor. The authors have recently shown that the novel second messenger, **sphingosine**, can block calcium release from skinned skeletal muscle fibers and from isolated skeletal muscle SR membranes (Sabbadini et al., J. Biol. Chemical 267: 15475-15484, 1992). In this report, the authors demonstrate that **sphingosine** also inhibits calcium release from isolated canine

cardiac SR membranes containing the ryanodine receptor when release is induced by caffeine, doxorubicin or by calcium. **Sphingosine** also prevents the augmentation of [3H]-ryanodine binding normally produced by caffeine and doxorubicin and exerts noncompetitive inhibition with regard to both releasing agents. **Sphingosine** significantly reduces in a dose-dependent manner [3H]-ryanodine binding to the high affinity site of the receptor and increases by several-fold the Kd for binding, which is consistent with a blocking action of **sphingosine** on the ryanodine receptor calcium channel. **Sphingosine** inhibits the extent of calcium-induced calcium release (CICR) and significantly shifts the threshold for CICR so that a higher level of trigger calcium is required to initiate CICR. The **sphingosine** inhibition of CICR is consistent with the near abolition of calcium dependent [3H]-ryanodine binding. HPLC anal. of **cardiac sphingosine** content indicates that **sphingosine** is present in the **cardiac** cell at moderately high levels (29.4 nmol/g wet wt for the entire cell and .apprx.0.4 μM for the cytosol) which are sufficient to produce significant inhibition by **sphingosine** on calcium release and ryanodine binding. The data suggest that **sphingosine** acts on the **cardiac** ryanodine receptor by opposing the physiol. stimulus (e.g. trigger calcium entering via the dihydropyridine receptor). The authors propose that **sphingosine** is produced by the T-tubule membranes and that **sphingosine** is released into the protected intracellular environment of the T-tubule/SR junction to neg. modulate calcium release. Consequently, it is possible that **sphingosine** is a physiol. relevant regulator of calcium levels in the **heart.**

L162 ANSWER 10 OF 23 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:253362 HCAPLUS
DOCUMENT NUMBER: 139:98589
TITLE: Expression and functional characterization of SCaMPER: A **sphingolipid**-modulated calcium channel of **cardiomyocytes**
AUTHOR(S): Cavalli, Amy L.; O'Brien, Nicole W.; Barlow, Steven B.; Betto, Romeo; Glembotski, Christopher C.; Palade, Philip T.; **Sabbadini, Roger A.**
CORPORATE SOURCE: SDSU Heart Institute and Department of Biology, San Diego State University, San Diego, CA, 92182-4614, USA
SOURCE: American Journal of Physiology (2003), 284(3, Pt. 1), C780-C790
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 02 Apr 2003
AB Calcium channels are important in a variety of cellular events including muscle contraction, signaling, proliferation, and apoptosis. **Sphingolipids** have been recognized as mediators of intracellular calcium release through their actions on a calcium channel, **sphingolipid** calcium release-mediating protein of the endoplasmic reticulum (SCaMPER). The current study investigates the expression and function of SCaMPER in **cardiomyocytes.** Northern analyses and RT-PCR cloning and sequencing revealed SCaMPER expression in both human and rat **cardiac** tissue. Immunofluorescence and Western blot analyses demonstrated that SCaMPER is abundant in **cardiac** tissue and is localized to the sarcotubular junction. This was confirmed by the colocalization of SCaMPER with dihydropyridine and ryanodine receptors by confocal microscopy. Purified T tubules were shown to contain SCaMPER and immunoelectron micrographs suggested that SCaMPER is located to the junctional T tubules, but a junctional SR localization cannot be ruled

out. The **sphingolipid** ligand for SCaMPER, **sphingosylphosphorylcholine** (SPC), initiated calcium release from the **cardiomyocyte** SR. Importantly, antisense knockdown of SCaMPER mRNA produced a substantial reduction of **sphingolipid** -induced calcium release, suggesting that SCaMPER is a potentially important calcium channel of **cardiomyocytes.**

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L162 ANSWER 11 OF 23 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-051708 [05] WPIX
CROSS REFERENCE: 2003-711671 [67]; 2003-831632 [77]; 2003-833248 [77]; 2003-844449 [78]; 2003-852794 [79]; 2003-852795 [79]; 2003-874920 [81]; 2003-875310 [81]; 2003-875896 [81]; 2003-900614 [82]; 2003-901592 [82]; 2004-033964 [03]; 2004-041349 [04]; 2004-041350 [04]; 2004-051566 [05]; 2004-060193 [06]; 2004-069239 [07]; 2004-080477 [08]; 2004-154329 [15]; 2005-478074 [48]
DOC. NO. CPI: C2004-020975
TITLE: Making composition comprising minicell useful in cancer therapy, where minicell displays archeabacterial membrane protein or membrane conjugate with membrane component chemically linked to conjugate such as toxin.
DERWENT CLASS: B04
INVENTOR(S): KLEPPER, R; **SABBADINI, R A**
PATENT ASSIGNEE(S): (KLEP-I) KLEPPER R; (SABB-I) SABBADINI R A
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2003219408	A1	20031127	(200405)*		242

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2003219408	A1 Provisional	US 2001-293566P	20010524
	Provisional	US 2002-359843P	20020225
	Div ex	US 2002-154951	20020524
		US 2002-157320	20020528

PRIORITY APPLN. INFO: US 2002-157320 20020528; US 2001-293566P 20010524; US 2002-359843P 20020225; US 2002-154951 20020524
ED 20040120
AB US2003219408 A UPAB: 20050728
NOVELTY - Making (M1) a composition comprising minicell, where minicell displays:

(a) membrane protein (P) chosen from eukaryotic, archeabacterial and organellar (P) or is a fusion protein having first polypeptide with transmembrane/membrane anchoring domain and second polypeptide not derived from eubacterial protein; and

(b) membrane conjugate having membrane component chemically linked to conjugated compound.

ACTIVITY - Cytostatic; Anorectic; Neuroleptic. No supporting data is given.

MECHANISM OF ACTION - None given.

USE - (M1) is useful for making a composition comprising a minicell (claimed). Minicells are useful for selective absorption of viral particles in the body. Minicells with fusion protein expressing antibodies to MUCH-1 or EGF-vIII are useful in cancer therapy. Minicells are useful for delivering therapeutic agents across the blood-brain barrier to the brain. Minicells are useful for delivering therapeutic agents e.g., anti-depressants and agents for the treatment of cancer, obesity, insomnia or schizophrenia. Minicells expressing receptors for toxic drugs are useful in treatment of drug overdoses. Minicells expressing muscarinic receptor are useful in the treatment of muscarine poisoning. Minicells are also used in automated in vitro determinations of compounds of interest such as ligands, proteins, small molecules, bioactive lipids, drugs, heavy metals and biological samples.
Dwg.0/2

L162 ANSWER 12 OF 23 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-875896 [81] WPIX
CROSS REFERENCE: 2003-711671 [67]; 2003-831632 [77]; 2003-833248 [77]; 2003-844449 [78]; 2003-852794 [79]; 2003-852795 [79]; 2003-874920 [81]; 2003-875310 [81]; 2003-900614 [82]; 2003-901592 [82]; 2004-033964 [03]; 2004-041349 [04]; 2004-041350 [04]; 2004-051566 [05]; 2004-051708 [05]; 2004-052155 [05]; 2004-060193 [06]; 2004-060537 [06]; 2004-069239 [07]; 2004-080477 [08]; 2004-154329 [15]; 2005-478074 [48]
DOC. NO. CPI: C2003-247338
TITLE: Pharmaceutical composition comprising minicells, useful for preventing, treating or diagnosing cancer, asthma or HIV, or as reagents in drug discovery and functional proteomics, as research tools or in compound screening.
DERWENT CLASS: B04 D16
INVENTOR(S): BERKLEY, N; KLEPPER, R; **SABBADINI, R A**
PATENT ASSIGNEE(S): (BERK-I) BERKLEY N; (KLEP-I) KLEPPER R; (SABB-I) SABBADINI R A
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2003207833	A1	20031106	(200381)*		243

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2003207833	A1 Provisional	US 2002-359843P	20020225
		US 2002-156811	20020528

PRIORITY APPLN. INFO: US 2002-359843P 20020225; US 2002-156811 20020528
ED 20031216
AB US2003207833 A UPAB: 20050728
NOVELTY - A pharmaceutical composition comprises a minicell that displays a membrane protein selected from a eukaryotic membrane protein, an archeabacterial membrane protein and an organellar membrane protein.
ACTIVITY - Cytostatic; Antiasthmatic; Antiallergic; Antiinflammatory; Gastrointestinal-Gen.; Antirheumatic; Antiarthritic; Osteopathic; Neuroprotective; Nootropic; Antidiabetic; Dermatological; Immunosuppressive; Antiparkinsonian; Antidepressant; Neuroleptic;

Anti-HIV; Virucide; Hepatotropic; Anticonvulsant; Antithyroid; Antibacterial; Antiparasitic.

No biological data given.

MECHANISM OF ACTION - Gene therapy; Cell therapy; Vaccine.

USE - The pharmaceutical composition and methods are useful in producing achromosomal and anucleate cells that are used as, e.g. therapeutics and/or diagnostics, reagents in drug discovery and functional proteomics, research tools, compound screening, and as agents for the delivery of nucleic acids and other bioactive compounds to cells. These may be used in preventing, treating or diagnosing cancer, asthma, allergies, bronchitis, inflammatory bowel disease, rheumatoid arthritis, osteoporosis, multiple sclerosis, diabetes, systemic lupus erythematosus, Alzheimer's disease, Parkinson's disease, depression, schizophrenia, HIV, hepatitis, Huntington's chorea, Grave's disease or infections (virus, bacteria or parasites).

Dwg.0/2

L162 ANSWER 13 OF 23 MEDLINE on STN DUPLICATE 1

ACCESSION NUMBER: 2006141823 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16530706
TITLE: Validation of an anti-**sphingosine**-1-phosphate antibody as a potential **therapeutic** in reducing growth, invasion, and **angiogenesis** in multiple tumor lineages.
AUTHOR: Visentin Barbara; Vekich John A; Sibbald Bradley J; Cavalli Amy L; Moreno Kelli M; Matteo Rosalia G; Garland William A; Lu Yiling; Yu Shuangxing; Hall Hassan S; Kundra Vikas; Mills Gordon B; **Sabbadini Roger A**
CORPORATE SOURCE: Department of Biology, San Diego State University, San Diego, California 92182, USA.
CONTRACT NUMBER: PO1 CA64602 (NCI)
R43 CA110298-01 (NCI)
SOURCE: Cancer cell, (2006 Mar) Vol. 9, No. 3, pp. 225-38.
Journal code: 101130617. ISSN: 1535-6108.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200604
ENTRY DATE: Entered STN: 14 Mar 2006
Last Updated on STN: 26 Apr 2006
Entered Medline: 25 Apr 2006

ED Entered STN: 14 Mar 2006
Last Updated on STN: 26 Apr 2006
Entered Medline: 25 Apr 2006

AB S1P has been proposed to contribute to cancer progression by regulating tumor proliferation, invasion, and **angiogenesis.** We developed a biospecific monoclonal antibody to S1P to investigate its role in tumorigenesis. The anti-S1P mAb substantially reduced tumor progression and in some cases eliminated measurable tumors in murine xenograft and allograft models. Tumor growth inhibition was attributed to antiangiogenic and antitumorigenic effects of the antibody. The anti-S1P mAb blocked EC migration and resulting capillary formation, inhibited blood vessel formation induced by VEGF and bFGF, and arrested tumor-associated **angiogenesis.** The anti-S1P mAb also neutralized S1P-induced proliferation, release of proangiogenic cytokines, and the ability of S1P to protect tumor cells from apoptosis in several tumor cell lines, validating S1P as a target for **therapy.**

L162 ANSWER 14 OF 23 MEDLINE on STN DUPLICATE 5

ACCESSION NUMBER: 2001557767 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11603928
TITLE: Apoptosis in the skeletal muscle of rats with **heart** failure is associated with increased serum levels of TNF-alpha and **sphingosine.**
AUTHOR: Dalla Libera L; **Sabbadini R**; Renken C; Ravara B; Sandri M; Betto R; Angelini A; Vescovo G
CORPORATE SOURCE: CNR Unit for Muscle Physiopathology, University of Padova, Padova, Italy.. ldl@civ.bio.unipd.it
CONTRACT NUMBER: IR25CPM58906-02 (NCI)
SOURCE: Journal of molecular and cellular cardiology, (2001 Oct) Vol. 33, No. 10, pp. 1871-8.
Journal code: 0262322. ISSN: 0022-2828.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 18 Oct 2001
Last Updated on STN: 24 Jan 2002
Entered Medline: 31 Dec 2001
ED Entered STN: 18 Oct 2001
Last Updated on STN: 24 Jan 2002
Entered Medline: 31 Dec 2001
AB Skeletal muscle in congestive **heart** failure (CHF) is responsible for increased fatigability, decreased endurance and exercise capacity. A specific myopathy with increased expression of fast myosin heavy chains (MHCs), myocyte atrophy, secondary to myocyte apoptosis, that is triggered by high levels of circulating tumor necrosis factor (TNF-alpha) has been described. However, a direct effect of TNF-alpha on skeletal muscle has not been described yet. In this paper we put forward the hypothesis that TNF-alpha plays an indirect effect on skeletal myocytes. In an animal model of CHF, the monocrotaline-**treated** rat, we have observed a significant (P<0.001) increase of circulating TNF-alpha that is paralleled by increased serum levels of the endogenous second messenger, **sphingosine** (SPH), (from 0.71+/-0.15 to 1.32+/-0.39 nmoles/ml, P<0.01). In the tibialis anterior (TA) muscle we found a marked increase of myocyte apoptosis (from 1.4+/-2.4 to 40.1+/-39.5 nuclei/mm(3), P<0.04). We correlated plasma levels of TNF-alpha with those of SPH and in turn with the magnitude of apoptosis. Linear regression showed a significant correlation between TNF-alpha, SPH, and apoptosis (r(2)=0.74, P=0.004 and r(2)=0.87, P=0.001 respectively). Analysis of covariance showed that TNF-alpha and SPH were independently correlated with the number of apoptotic nuclei (P=0.0001). In parallel in vitro experiments, where increasing concentrations of SPH were applied to skeletal muscle cells in culture, we observed a dose-dependent increase in apoptosis. These results suggest that TNF-alpha-induced SPH production may be responsible for skeletal muscle apoptosis. The link between TNF-alpha and skeletal muscle apoptosis could be represented by the second messenger SPH, which can directly induce apoptosis in these cells.

L162 ANSWER 15 OF 23 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 95173984 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7869389
TITLE: **Sphingosine** effects on the contractile behavior of skinned **cardiac** myocytes.
AUTHOR: Webster R J; **Sabbadini R A**; Dettbarn C A; Paolini P J
CORPORATE SOURCE: Department of Biology, San Diego State University, CA

92182.
CONTRACT NUMBER: HL42527 (NHLBI)
SOURCE: Journal of molecular and cellular cardiology, (1994 Oct) Vol. 26, No. 10, pp. 1273-90.
Journal code: 0262322. ISSN: 0022-2828.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 7 Apr 1995
Last Updated on STN: 6 Feb 1998
Entered Medline: 27 Mar 1995
ED Entered STN: 7 Apr 1995
Last Updated on STN: 6 Feb 1998
Entered Medline: 27 Mar 1995
AB **Sphingosine** modulates myocyte beating behavior by acting on the sarcoplasmic reticulum calcium release channel, the ryanodine receptor. Chemically skinned myocytes isolated from adult rabbit ventricles exhibited spontaneous asynchonous contractions in response to micromolar levels of calcium. These cells do not have a functional sarcolemma but exhibit spontaneous contraction-relaxation cycles which are controlled by the sarcoplasmic reticulum. The intracellular second messenger, **sphingosine**, significantly reduced myocyte beat frequency in a biphasic manner with an IC50 of c. 0.5 microM. A computerized video-enhancement micrography system was used to determine the effect of **sphingosine** on sarcomere contractile parameters and to determine the potential source of the altered beating behavior produced by **sphingosine.** Contraction parameters related to sarcomere shortening were unaffected by **sphingosine** in the submicromolar range, suggesting that **sphingosine** had no effect on the contractile machinery itself. However, submicromolar **sphingosine** had a significant inhibitory effect on the spread of activation from sarcomere to sarcomere in these cells. Activation waves were propagated with an average velocity of 331 and 199 microns/s in control and **sphingosine** (0.58 microM) **treated** cells, respectively. Permeabilized myocyte calcium uptake was markedly increased by **treatment** with **sphingosine**, consistent with an inhibitory effect of **sphingosine** on sarcoplasmic reticulum calcium release. **Sphingosine** blocked calcium-induced calcium release from isolated **cardiac** sarcoplasmic reticulum membranes containing the ryanodine receptor. The results suggest that the site of **sphingosine** action on calcium signaling and beating behavior in the **cardiac** cell is the sarcoplasmic reticulum ryanodine receptor. By inhibiting channel opening **sphingosine** may increase the calcium threshold necessary to trigger calcium-induced calcium release, thus modulating **cardiac** excitation-contraction coupling.

L162 ANSWER 16 OF 23 MEDLINE on STN
ACCESSION NUMBER: 2001016755 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10971577
TITLE: Expression and characterization of Edg-1 receptors in rat **cardiomyocytes**: calcium deregulation in response to **sphingosine** 1-phosphate.
AUTHOR: Nakajima N; Cavalli A L; Biral D; Glembotski C C; McDonough P M; Ho P D; Betto R; Sandona D; Palade P T; Dettbarn C A; Klepper R E; **Sabbadini R A**
CORPORATE SOURCE: Department of Biology and Heart Institute, San Diego State University, CA 92182-4614, USA.

CONTRACT NUMBER: HL 63975 (NHLBI)
NS/HL 25037 (NINDS)
SOURCE: European journal of biochemistry / FEBS, (2000 Sep) Vol. 267, No. 18, pp. 5679-86.
Journal code: 0107600. ISSN: 0014-2956.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 7 Nov 2000

ED Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 7 Nov 2000

AB Recent evidence indicates that **sphingolipids** are produced by the **heart** during hypoxic stress and by blood platelets during thrombus formation. It is therefore possible that **sphingolipids** may influence **heart** cell function by interacting with G-protein-coupled receptors of the Edg family. In the present study, it was found that **sphingosine** 1-phosphate (Sph1P), the prototypical ligand for Edg receptors, produced calcium overload in rat **cardiomyocytes.** The cDNA for Edg-1 was cloned from rat **cardiomyocytes** and, when transfected in an antisense orientation, effectively blocked Edg-1 protein expression and reduced the Sph1P-mediated calcium deregulation. Taken together, these results demonstrate that **cardiomyocytes** express an extracellular lipid-sensitive receptorsystem that can respond to **sphingolipid** mediators. Because the major source of Sph1P is from blood platelets, we speculate that Edg-mediated Sph1P negative inotropic and **cardiotoxic** effects may play important roles in acute **myocardial ischemia** where Sph1P levels are probably elevated in response to thrombus.

L162 ANSWER 17 OF 23 MEDLINE on STN
ACCESSION NUMBER: 2000436930 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10937863
TITLE: The role of **sphingolipids** in the control of skeletal muscle function: a review.
AUTHOR: **Sabbadini R A**; Danieli-Betto D; Betto R
CORPORATE SOURCE: Department of Biology and Heart Institute, San Diego State University, CA 92182, USA.
SOURCE: Italian journal of neurological sciences, (1999 Dec) Vol. 20, No. 6, pp. 423-30. Ref: 87
Journal code: 8006502. ISSN: 0392-0461.
PUB. COUNTRY: Italy
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 28 Sep 2000
Last Updated on STN: 28 Sep 2000
Entered Medline: 20 Sep 2000

ED Entered STN: 28 Sep 2000
Last Updated on STN: 28 Sep 2000
Entered Medline: 20 Sep 2000

AB In this review, potential roles for the endogenous **sphingolipid**, **sphingosine**, and its derivatives are described for muscle cells.

Sphingosine modulates the function of important calcium channels in muscle, including the ryanodine receptor (RyR) calcium release channel of the sarcoplasmic reticulum (SR). **Sphingosine** blocks calcium release through the SR ryanodine receptor and reduces the activity of single skeletal muscle RyR channels reconstituted into planar lipid bilayers. **Sphingosine**-blocked calcium release is coincident with the inhibitory effects of **sphingosine** on [3H]ryanodine binding to the RyR. The **sphingomyelin** signal transduction pathway has also been identified in both skeletal and **cardiac** muscle. A neutral form of **sphingomyelinase** (nSMase) enzyme has been localized to the junctional transverse tubule membrane. The high turnover of the SMase is responsible for the production of ceramide and **sphingosine.** HPLC analyses indicate that significant resting levels of **sphingosine** are present in muscle tissue. A model of excitation-contraction coupling is presented suggesting a potential role for this endogenous **sphingolipid** in normal muscle function. Putative roles for **sphingolipid** mediators in skeletal muscle dysfunction are also discussed. We hypothesize that **sphingosine** plays important roles in malignant hyperthermia and during the development of muscle fatigue.

L162 ANSWER 18 OF 23 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 1998122954 EMBASE
TITLE: MKK6 activates **myocardial** cell NF-κB and inhibits apoptosis in a p38 mitogen-activated protein kinase-dependent manner.
AUTHOR: Zechner D.; Craig R.; Hanford D.S.; McDonough P.M.; **Sabbadini R.A.**; Glembotski C.C.
CORPORATE SOURCE: C.C. Glembotski, Dept. of Biology, San Diego State University, San Diego, CA 92182, United States. cglembotski@sunsrteoke.sdsu.edu
SOURCE: Journal of Biological Chemistry, (3 Apr 1998) Vol. 273, No. 14, pp. 8232-8239. .
Refs: 76
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 7 May 1998
Last Updated on STN: 7 May 1998
ED Entered STN: 7 May 1998
Last Updated on STN: 7 May 1998

AB In **cardiac** myocytes the stimulation of p38 mitogen-activated protein kinase activates a hypertrophic growth program and the induction of the **cardiac**-specific genes associated with this program. This study focused on determining whether these novel growth-promoting effects are accompanied by the p38-mediated inhibition of apoptosis, and if so, what signaling pathways might be responsible. Primary neonatal rat ventricular myocytes were driven into apoptosis by **treatments** known to induce apoptosis in other cell types, e.g. incubation with anisomycin or overexpression constitutively active MEKK- 1 (MEKK-1(COOH)), a protein that strongly activates extracellular signal- regulated kinase and N-terminal c-Jun kinase, but not p38. Overexpression of constitutively active MKK6, MKK6 (Glu), which selectively activates p38 in **cardiac** myocytes, protected cells from either anisomycin- or MEKK-1(COOH)- induced apoptosis. This protection was blocked by SB

203580, a selective p38 inhibitor. MKK6 (Glu) also activated transcription mediated by NF-κB, a factor which protects other cell types from apoptosis. The activation of NF- κB and the protection from apoptosis mediated by MKK6 (Glu) were both blocked by SB 203580. Interestingly, overexpression of a mutant form of I- κBα, which inhibits nuclear translocation of NF-κB, completely blocked MKK6 (Glu)-activated NF-κB but had little effect on MKK6s anti-apoptotic effects. These findings suggest that, in part, the overexpression of MKK6 (Glu) may foster growth and survival of **cardiac** myocytes by protecting them from apoptosis in a p38-dependent manner. Additionally, while NF-κB is activated in **myocardial** cells by p38, this does not appear to be the major mechanism by which MKK6 (Glu) exerts its anti-apoptotic effects in this cell type, suggesting a novel pathway for p38-mediated protection from apoptosis.

L162 ANSWER 19 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:224959 BIOSIS
DOCUMENT NUMBER: PREV200600224527
TITLE: Compositions and methods for the **treatment** and **prevention** of cardiovascular diseases and disorders, and for identifying agents **therapeutic** therefor.
AUTHOR(S): **Sabbadini, Roger A.** [Inventor]
CORPORATE SOURCE: Lakeside, CA USA
ASSIGNEE: Medlyte, Inc., SDSU Heart Institute
PATENT INFORMATION: US 06881546 20050419
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (APR 19 2005)
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Apr 2006
Last Updated on STN: 5 Apr 2006
ED Entered STN: 5 Apr 2006
Last Updated on STN: 5 Apr 2006
AB Methods and compositions are disclosed that are useful for the **prevention** and/or **treatment** of cardiovascular and cardiac diseases and disorders, or damage resulting from surgical or **medical** procedures that may cause ischemic or ischemic/reperfusion damage in humans; and cardiovascular trauma. The beneficial effects of the compositions and methods are achieved through the use of **pharmaceutical** compositions that include agents that interfere with the production and/or biological activities of **sphingolipids** and their metabolites, particularly **sphingosine** (SPH) and **sphingosine**-1-phosphate (S-1-P). Also disclosed are methods for identifying and isolating **therapeutic** agents.

L162 ANSWER 20 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:58217 BIOSIS
DOCUMENT NUMBER: PREV200600046494
TITLE: Increased functional recovery after myocardial infarction in mice **treated** with antibody to **sphingosine**-1-phosphate.
AUTHOR(S): Lowe, Nicole Gellings [Reprint Author]; Matteo, Rosalie G.; Broyde, Anatoly; Moreno, Kell M.; Sussman, Mark A.; **Sabbadini, Roger A.**
CORPORATE SOURCE: San Diego State Univ, San Diego, CA 92182 USA

SOURCE: Circulation, (OCT 25 2005) Vol. 112, No. 17, Suppl. S, pp. U155.
Meeting Info.: 78th Annual Scientific Session of the American-Heart-Association. Dallas, TX, USA. November 13 -16, 2005. Amer Heart Assoc.
CODEN: CIRCAZ. ISSN: 0009-7322.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Jan 2006
Last Updated on STN: 4 Jan 2006
ED Entered STN: 4 Jan 2006
Last Updated on STN: 4 Jan 2006

L162 ANSWER 21 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:185264 BIOSIS
DOCUMENT NUMBER: PREV200100185264
TITLE: **Sphingosine**-1-phosphate is an early serum marker for acute myocardial infarction (AMI).
AUTHOR(S): Carstens, Jeffrey S. [Reprint author]; Deutschman, Douglas H.; Page, M. Trevor; Klepper, Robert E.; **Sabbadini, Roger A.**
CORPORATE SOURCE: San Diego State University, San Diego, CA, USA
SOURCE: Journal of the American College of Cardiology, (February, 2001) Vol. 37, No. 2 Supplement A, pp. 354A. print.
Meeting Info.: 50th Annual Scientific Session of the American College of Cardiology. Orlando, Florida, USA. March 18-21, 2001. American College of Cardiology.
CODEN: JACCDI. ISSN: 0735-1097.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Apr 2001
Last Updated on STN: 18 Feb 2002
ED Entered STN: 20 Apr 2001
Last Updated on STN: 18 Feb 2002

L162 ANSWER 22 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:288156 BIOSIS
DOCUMENT NUMBER: PREV200200288156
TITLE: The MIRF trial: **Sphingosine**-1-phosphate (S1P) as a novel marker for myocardial ischemia.
AUTHOR(S): Deutschman, Douglas [Reprint author]; Carstens, Jeffrey; Page, M. Trevor; Klepper, Robert; Chastain, Hollace; **Sabbadini, Roger**
CORPORATE SOURCE: San Diego State Univ, San Diego, CA, USA
SOURCE: Circulation, (October 23, 2001) Vol. 104, No. 17 Supplement, pp. II.485. print.
Meeting Info.: Scientific Sessions 2001 of the American Heart Association. Anaheim, California, USA. November 11-14, 2001. American Heart Association.
CODEN: CIRCAZ. ISSN: 0009-7322.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 15 May 2002
Last Updated on STN: 15 May 2002
ED Entered STN: 15 May 2002

Last Updated on STN: 15 May 2002

L162 ANSWER 23 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:117171 BIOSIS
DOCUMENT NUMBER: PREV200100117171
TITLE: The MIRF Trial: Predicting the incidence and severity of CAD using serum **sphingolipids.**
AUTHOR(S): **Sabbadini, Roger A.** [Reprint author]; Deutschman, Douglas H. [Reprint author]; Carstens, Jeffrey S.; Klepper, Robert L.; Smith, Wyatt S.; Chastain, Hollace D.; Page, Trevor; Nakajima, Nobuko; Young, Thomas R.
CORPORATE SOURCE: San Diego State Univ, San Diego, CA, USA
SOURCE: Circulation, (October 31, 2000) Vol. 102, No. 18 Supplement, pp. II.699. print.
Meeting Info.: Abstracts from American Heart Association Scientific Sessions 2000. New Orleans, Louisiana, USA. November 12-15, 2000. American Heart Association.
CODEN: CIRCAZ. ISSN: 0009-7322.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Mar 2001
Last Updated on STN: 15 Feb 2002
ED Entered STN: 7 Mar 2001
Last Updated on STN: 15 Feb 2002

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FILE 'STNGUIDE' ENTERED AT 13:53:45 ON 11 JUL 2006
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LAST RELOADED: Jul 7, 2006 (20060707/UP).

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               E US2001-29372/APPS

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     FILE 'HCAPLUS' ENTERED AT 10:20:52 ON 11 JUL 2006
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L7             QUE ABB=ON  PLU=ON  AY<2001 OR PY<2001 OR PRY<2001 OR MY<2001
               OR REVIEW/DT
L8             QUE ABB=ON  PLU=ON  AY<2001 OR PY<2001 OR PRY<2001
L9             QUE ABB=ON  PLU=ON  ?ENZYM?
L10            QUE ABB=ON  PLU=ON  ?SPHINGO? OR ?CERAMID? OR KETOSPHING? OR
               GALACTOSYLCERAMID? OR DIHYDROCERAMID?
L11            QUE ABB=ON  PLU=ON  CEREBROSID? OR ?PALMITOYLTRANSFER? OR
               (?PALMITOYL?(1A)TRANSFERAS?) OR (NADPH(3A)REDUCTAS?)
L12            QUE ABB=ON  PLU=ON  HEART? OR ?CORONAR? OR ?CARDIO? OR
               ?CARDIA? OR MYOCARD?
L13            QUE ABB=ON  PLU=ON  ISCHEM? OR POSTISCHEM? OR REPERFUS? OR
               NEOVASCUL? OR (NEO(W)VASCUL?) OR ANGIOGEN? OR (ANGIO(W)GENE?)
               OR STENT? OR ?STENOSIS? OR RESTENOSIS? OR STROKE?
L14            QUE ABB=ON  PLU=ON  ?CEREBR? OR BRAIN
L15            QUE ABB=ON  PLU=ON  VASCU? OR VEIN? OR ARTER?
L16            QUE ABB=ON  PLU=ON  ARTERY+PFT,OLD,NT/CT
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L17             QUE ABB=ON  PLU=ON  HEART+PFT,OLD,NT/CT
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L20             QUE ABB=ON  PLU=ON  ISCHEMIA+PFT,OLD,NT/CT
L21             QUE ABB=ON  PLU=ON  STROKE+PFT,OLD,NT/CT
L22             QUE ABB=ON  PLU=ON  "HEART, DISEASE"+PFT,OLD,NT/CT
L23             QUE ABB=ON  PLU=ON  REPERFUSION+PFT,OLD,NT/CT
L24             QUE ABB=ON  PLU=ON  "BRAIN, DISEASE"+PFT,OLD,NT/CT
L25             QUE ABB=ON  PLU=ON  ANGIOGENESIS+PFT,OLD,NT/CT
L26             QUE ABB=ON  PLU=ON  "CARDIOVASCULAR SYSTEM, DISEASE"+PFT,OLD,NT
                /CT
                E CEREBROVASCUL/CT
                E E32+ALL
L27             QUE ABB=ON  PLU=ON  CERAMIDES+PFT,OLD,NT/CT
L28             QUE ABB=ON  PLU=ON  SPHINGOMYELINS+PFT,OLD,NT/CT
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                E ENZYMES/CT
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L31             QUE ABB=ON  PLU=ON  SPHINGOLIPIDS+PFT,OLD,NT/CT
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L34             QUE ABB=ON  PLU=ON  IMPED? OR REDUC? OR DEPRESS? OR REPRESS?
                OR SUPPRESS? OR INHIBIT? OR PROHIBIT? OR ANTAGON? OR PREVENT?
                OR INTERRUPT? OR DISRUPT? OR RETARD? OR SLOW? OR BLOCK? OR
                TERMINAT? OR RESTRICT? OR STOP?
L35             QUE ABB=ON  PLU=ON  AGON? OR PROMOT? OR ELICIT? OR ENCOURAG?
                OR STIMULAT? OR CAUSE OR CAUSED OR CAUSES OR CAUSING OR
                EFFECTS OR EFFECTED OR EFFECTING OR EFFECT OR ENHANC? OR
                AMPLIF? OR ACCELERAT?

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                L32) OR L11)
L37           15 SEA ABB=ON  PLU=ON  L36 AND ((L12 OR L13 OR L14 OR L15) OR
                (L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26))
L38             QUE ABB=ON  PLU=ON  ENZYM?/CW
L39            2 SEA ABB=ON  PLU=ON  L37 AND ((L29 OR L30) OR L38 OR L9)
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    FILE 'STNGUIDE' ENTERED AT 10:45:52 ON 11 JUL 2006

    FILE 'HCAPLUS' ENTERED AT 10:46:25 ON 11 JUL 2006
L40           15 SEA ABB=ON  PLU=ON  L37 AND (L27 OR L28 OR (L31 OR L32))
L41             QUE ABB=ON  PLU=ON  ?SPHINGO?
L42           15 SEA ABB=ON  PLU=ON  L37 AND L41
L43           10 SEA ABB=ON  PLU=ON  L42 AND (?SPHINGO?/CW)
L44           10 SEA ABB=ON  PLU=ON  L39 OR L43
                SAVE TEMP L44 GIT372HCAINV/A
                D SCAN

    FILE 'STNGUIDE' ENTERED AT 10:48:13 ON 11 JUL 2006

    FILE 'ZCAPLUS' ENTERED AT 10:50:10 ON 11 JUL 2006
L45             QUE ABB=ON  PLU=ON  "ARTERY, DISEASE"+PFT,OLD,NT/CT
L46             QUE ABB=ON  PLU=ON  INDUC?
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     FILE 'HCAPLUS' ENTERED AT 10:51:02 ON 11 JUL 2006
L47      294015 SEA ABB=ON  PLU=ON  ((L29 OR L30) OR L38)(L)(L9 OR L10 OR L41)

L48       90457 SEA ABB=ON  PLU=ON  ((L29 OR L30) OR L38)(L)(L33 OR L34 OR L35
                OR L46)
L49       90456 SEA ABB=ON  PLU=ON  L47 AND L48
L50        7859 SEA ABB=ON  PLU=ON  (L19 OR (L20 OR L21 OR L22 OR L23 OR L24
                OR L25 OR L26) OR L45)(L) (L9 OR L10 OR L41)
L51        7098 SEA ABB=ON  PLU=ON  (L27 OR L28 OR (L31 OR L32) OR (?SPHINGO?/C
                W))(L)(L12 OR L13 OR L14 OR L15)
L52         589 SEA ABB=ON  PLU=ON  L49 AND (L50 OR L51)
L53         431 SEA ABB=ON  PLU=ON  L52 AND L7
L54         738 SEA ABB=ON  PLU=ON  ((L29 OR L30) OR L38)(L)(L10 OR L11 OR
                L41)
L55         378 SEA ABB=ON  PLU=ON  L48 AND L54
L56          17 SEA ABB=ON  PLU=ON  L55 AND (L50 OR L51)
L57          12 SEA ABB=ON  PLU=ON  L56 AND L7
L58          11 SEA ABB=ON  PLU=ON  L57 NOT L44
                D SCAN TI HIT

     FILE 'STNGUIDE' ENTERED AT 10:56:34 ON 11 JUL 2006

     FILE 'HCAPLUS' ENTERED AT 10:57:30 ON 11 JUL 2006
L59          721 SEA ABB=ON  PLU=ON  (L19 OR (L20 OR L21 OR L22 OR L23 OR L24
                OR L25 OR L26) OR L45)(L) (L10 OR L11 OR L41)
L60        7098 SEA ABB=ON  PLU=ON  (L27 OR L28 OR (L31 OR L32) OR (?SPHINGO?/C
                W))(L) ((L12 OR L13 OR L14 OR L15))
L61         738 SEA ABB=ON  PLU=ON  ((L29 OR L30) OR L38)(L)(L41 OR L10 OR
                L11)
L62         263 SEA ABB=ON  PLU=ON  L59 AND ((L60 OR L61))
L63         180 SEA ABB=ON  PLU=ON  L62 AND L7
L64       10303 SEA ABB=ON  PLU=ON  (L33 OR L34 OR L35 OR L46)(10A) L41
L65          62 SEA ABB=ON  PLU=ON  L63 AND L64
L66          55 SEA ABB=ON  PLU=ON  L63 AND L4
L67          77 SEA ABB=ON  PLU=ON  L65 OR L66
L68          73 SEA ABB=ON  PLU=ON  L67 NOT L5
L69          60 SEA ABB=ON  PLU=ON  L68 AND (?SPHINGO?/OBI)

     FILE 'STNGUIDE' ENTERED AT 11:04:24 ON 11 JUL 2006
L*** DEL         QUE TREAT? OR ?THERAP? OR MEDIC? OR PHARM?

     FILE 'ZCAPLUS' ENTERED AT 11:06:08 ON 11 JUL 2006
L70              QUE ABB=ON  PLU=ON  TREAT? OR ?THERAP? OR MEDIC? OR PHARM?
L71              QUE ABB=ON  PLU=ON  PREVENT? OR AVOID?

     FILE 'HCAPLUS' ENTERED AT 11:06:53 ON 11 JUL 2006
L*** DEL      24 S L68 AND (L71 OR L70)
L72              QUE ABB=ON  PLU=ON  ADMIN?
L73           26 SEA ABB=ON  PLU=ON  L67 AND ((L70 OR L71 OR L72))
L74           25 SEA ABB=ON  PLU=ON  L73 NOT L5
                D SCAN TI HIT

     FILE 'STNGUIDE' ENTERED AT 11:08:45 ON 11 JUL 2006

     FILE 'HCAPLUS' ENTERED AT 11:12:57 ON 11 JUL 2006
L75           77 SEA ABB=ON  PLU=ON  L67 AND L41
L76           26 SEA ABB=ON  PLU=ON  L73 AND L41
L77           77 SEA ABB=ON  PLU=ON  L67 OR L75
                SAVE TEMP L77 GIT372HCAP/A
L78           26 SEA ABB=ON  PLU=ON  L73 OR L76
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                SAVE TEMP L78 GIT372HCA1B/A

     FILE 'STNGUIDE' ENTERED AT 11:14:44 ON 11 JUL 2006
                D SAVED

     FILE 'ZCAPLUS' ENTERED AT 11:32:41 ON 11 JUL 2006
L79             QUE ABB=ON  PLU=ON  SMASE
L80             QUE ABB=ON  PLU=ON  SPHINGOMYELINAS?

     FILE 'WPIX' ENTERED AT 11:33:35 ON 11 JUL 2006
L81             QUE ABB=ON  PLU=ON  (B14-F? OR C14-F?)/MC
L82          472 SEA ABB=ON  PLU=ON  ((ALTER/BIX OR ALTERS/BIX OR ALTERED/BIX
                OR ALTERING/BIX OR MODERAT?/BIX OR MODULAT?/BIX OR REGULAT?/BIX
                 OR CONTROL?/BIX OR MEDIAT?/BIX) OR (IMPED?/BIX OR REDUC?/BIX
                OR DEPRESS?/BIX OR REPRESS?/BIX OR SUPPRESS?/BIX OR INHIBIT?/BI
                X OR PROHIBIT?/BIX OR ANTAGON?/BIX OR PREVENT?/BIX OR INTERRUPT
                ?/BIX OR DISRUPT?/BIX OR RETARD?/BIX OR SLOW?/BIX OR BLOCK?/BIX
                 OR TERMINAT?/BIX OR RESTRICT?/BIX OR STOP?/BIX) OR (INDUC?/BIX
                ))(15A)((?SPHINGO?/BIX) OR (SMASE/BIX) OR (SPHINGOMYELINAS?/BIX
                ))
L83          142 SEA ABB=ON  PLU=ON  L82 AND L81
                D TRI 130-135
L84            1 SEA ABB=ON  PLU=ON  L5 AND L82
L85            4 SEA ABB=ON  PLU=ON  L5 AND ?SPHINGO?/BIX
                SAVE TEMP L85 GIT372WPIINV/A
                D TRI 1-4

     FILE 'STNGUIDE' ENTERED AT 11:41:21 ON 11 JUL 2006

     FILE 'ZCAPLUS' ENTERED AT 11:43:11 ON 11 JUL 2006
L86             QUE ABB=ON  PLU=ON  C12N009/IPC
                E C12N009-00/IPC
                E E53+ALL
L87             QUE ABB=ON  PLU=ON  C12N009-99/IPC

     FILE 'WPIX' ENTERED AT 11:44:35 ON 11 JUL 2006
L88            22 SEA ABB=ON  PLU=ON  L83 AND L86
L89             QUE ABB=ON  PLU=ON  A61P?/IPC
                D TRI L88 15-22
                D QUE L82
L90           238 SEA ABB=ON  PLU=ON  L82 AND L8
L91            41 SEA ABB=ON  PLU=ON  L90 AND L86
L92            88 SEA ABB=ON  PLU=ON  L90 AND (L81 OR L89)
L93            22 SEA ABB=ON  PLU=ON  L91 AND L92
L94            21 SEA ABB=ON  PLU=ON  L93 NOT L85
                D TRI 10-21

     FILE 'STNGUIDE' ENTERED AT 12:01:34 ON 11 JUL 2006

     FILE 'WPIX' ENTERED AT 12:02:39 ON 11 JUL 2006
L95            16 SEA ABB=ON  PLU=ON  L93 AND ((HEART?/BIX OR ?CORONAR?/BIX OR
                ?CARDIO?/BIX OR ?CARDIA?/BIX OR MYOCARD?/BIX) OR (ISCHEM?/BIX
                OR POSTISCHEM?/BIX OR REPERFUS?/BIX OR NEOVASCUL?/BIX OR
                (NEO/BIX(W)VASCUL?/BIX) OR ANGIOGEN?/BIX OR (ANGIO/BIX(W)GENE?/
                BIX) OR STENT?/BIX OR ?STENOSIS?/BIX OR RESTENOSIS?/BIX OR
                STROKE?/BIX) OR (?CEREBR?/BIX OR BRAIN/BIX) OR (VASCU?/BIX OR
                VEIN?/BIX OR ARTER?/BIX))
L96            22 SEA ABB=ON  PLU=ON  L93 AND (?SPHINGO?/BIX OR (SMASE/BIX) OR
                (SPHINGOMYELINAS?/BIX) OR (?SPHINGO?/BIX OR ?CERAMID?/BIX OR
                KETOSPHING?/BIX OR GALACTOSYLCERAMID?/BIX OR DIHYDROCERAMID?/BI
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               X) OR (CEREBROSID?/BIX OR ?PALMITOYLTRANSFER?/BIX OR (?PALMITOY
               L?/BIX(1A)TRANSFERAS?/BIX) OR (NADPH/BIX(3A)REDUCTAS?/BIX)))
L97          22 SEA ABB=ON  PLU=ON  L93 OR L95 OR L96
               D TRI 8-12
               SAVE TEMP L97 GIT372WPI1B/A

     FILE 'STNGUIDE' ENTERED AT 12:05:44 ON 11 JUL 2006
               D SAVED

     FILE 'MEDLINE' ENTERED AT 12:20:56 ON 11 JUL 2006
L98          19 SEA ABB=ON  PLU=ON  L5 AND ?SPHINGO?
L99          14 SEA ABB=ON  PLU=ON  L98 AND (L12 OR L13 OR L14 OR L15)
               D TRI 1-14
L100         11 SEA ABB=ON  PLU=ON  L99 AND (L70 OR L71 OR L72)
               D TRI 1-11
               SAVE TEMP L100 GIT372MEDINV/A
L101           QUE ABB=ON  PLU=ON  SPHINGOLIPIDS+PFT,OLD,NT/CT
L102      16230 SEA ABB=ON  PLU=ON  (L33 OR L34 OR L35 OR L46)(10A)(L41 OR L79
               OR L80 OR L10 OR L11 OR ?SPHINGO?)
L103     354457 SEA ABB=ON  PLU=ON  (L70 OR L71 OR L72) (10A)(L12 OR L13 OR
               L14 OR L15)
L104        360 SEA ABB=ON  PLU=ON  L102 AND L103
L105        217 SEA ABB=ON  PLU=ON  L104 AND L7
L106         25 SEA ABB=ON  PLU=ON  L105 AND L4
L107         82 SEA ABB=ON  PLU=ON  L105 AND (L101 OR ((?SPHINGO?/TI,IT,CC,CT,S
               T,STP) OR (SMASE/TI,IT,CC,CT,ST,STP) OR (SPHINGOMYELINAS?/TI,IT
               ,CC,CT,ST,STP)))
L108         82 SEA ABB=ON  PLU=ON  L106 OR L107
               D TRI 70-80
               E SPHINGO/CT
L109         58 SEA ABB=ON  PLU=ON  L105 AND L101
L110         77 SEA ABB=ON  PLU=ON  L106 OR L109
               D TRI 60-77
               D QUE
               D TRI L100 1-11
L111         77 SEA ABB=ON  PLU=ON  L108 AND ((L10 OR L11 OR L41 OR L79 OR
               L80)(L)(L72 OR L70))
L112         28 SEA ABB=ON  PLU=ON  L108 AND ((L12 OR L13 OR L14 OR L15)(L)(DE
               OR DT))
L113         27 SEA ABB=ON  PLU=ON  L111 AND L112
L114         28 SEA ABB=ON  PLU=ON  (L112 OR L113)
L115         28 SEA ABB=ON  PLU=ON  L114 NOT L100
L116         25 SEA ABB=ON  PLU=ON  L106 NOT L100
L117         41 SEA ABB=ON  PLU=ON  L114 OR L106
               D TRI L114 10-20
L118         22 SEA ABB=ON  PLU=ON  L117 AND L101
               D TRI 10-22
L119         31 SEA ABB=ON  PLU=ON  L114 OR L118
               SAVE TEMP L119 GIT372MED1B/A

     FILE 'EMBASE' ENTERED AT 12:43:56 ON 11 JUL 2006
L120         19 SEA ABB=ON  PLU=ON  L5 AND ?SPHINGO?
L121         19 SEA ABB=ON  PLU=ON  L5 AND (?SPHINGO? OR L79 OR L80)
L122         15 SEA ABB=ON  PLU=ON  L121 AND (L12 OR L13 OR L14 OR L15)
L123          9 SEA ABB=ON  PLU=ON  L122 AND (L70 OR L71 OR L72)
               SAVE TEMP L123 GIT372EMBINV/A
               D TRI 1-9

     FILE 'STNGUIDE' ENTERED AT 12:45:48 ON 11 JUL 2006
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     FILE 'ZCAPLUS' ENTERED AT 12:47:07 ON 11 JUL 2006
L124            QUE ABB=ON  PLU=ON  DISEAS? OR DISORDER? OR CONDITION? OR
                SYNDROM? OR INFARC? OR COMPLICAT? OR FAILUR?
L125            QUE ABB=ON  PLU=ON  INJUR?

     FILE 'EMBASE' ENTERED AT 12:48:58 ON 11 JUL 2006
L126       13187 SEA ABB=ON  PLU=ON  (L33 OR L34 OR L35 OR L46)(10A)(L10 OR L11
                OR L41 OR L79 OR L80)
L*** DEL   58480 S (L70-L71)(10A)L13
L127       62033 SEA ABB=ON  PLU=ON  ((L70 OR L71 OR L72))(10A)L13
L128        5359 SEA ABB=ON  PLU=ON  ((L70 OR L71 OR L72))(10A)((L12 OR
                L14)(10A)L125)
L129          55 SEA ABB=ON  PLU=ON  L126 AND (L127 OR L128)
L130         103 SEA ABB=ON  PLU=ON  (L127 OR L128) AND L4
L131          75 SEA ABB=ON  PLU=ON  (L129 OR L130) AND L7
                D TRI 60-670

     FILE 'STNGUIDE' ENTERED AT 12:52:38 ON 11 JUL 2006

     FILE 'EMBASE' ENTERED AT 12:53:14 ON 11 JUL 2006

     FILE 'ZCAPLUS' ENTERED AT 12:53:18 ON 11 JUL 2006
L132            QUE ABB=ON  PLU=ON  ?ISCHAEM?

     FILE 'EMBASE' ENTERED AT 12:53:39 ON 11 JUL 2006
L133          15 SEA ABB=ON  PLU=ON  L126 AND L132
L134          87 SEA ABB=ON  PLU=ON  L131 OR L133
L135          79 SEA ABB=ON  PLU=ON  L134 AND L7
L136          10 SEA ABB=ON  PLU=ON  L135 AND (L41 OR L79 OR L80)
                D TRI 1-10

     FILE 'STNGUIDE' ENTERED AT 12:54:55 ON 11 JUL 2006
                D QUE

     FILE 'EMBASE' ENTERED AT 12:56:47 ON 11 JUL 2006
L137          48 SEA ABB=ON  PLU=ON  (L127 OR L128) AND (L41 OR L79 OR L80)
L*** DEL    6261 S L127-L128 AND (L41 OR L79 OR L80 OR L9 OR L10)
L*** DEL    2421 S L138 AND L7
L138         101 SEA ABB=ON  PLU=ON  (L127 OR L128) AND (L41 OR L79 OR L80 OR
                L10 OR L11)
L139          41 SEA ABB=ON  PLU=ON  L138 AND L7
L140          43 SEA ABB=ON  PLU=ON  L136 OR L139
                D TRI 30-43

     FILE 'STNGUIDE' ENTERED AT 12:59:23 ON 11 JUL 2006

     FILE 'EMBASE' ENTERED AT 13:00:27 ON 11 JUL 2006
                SAVE TEMP L140 GIT372EMB1B/A

     FILE 'STNGUIDE' ENTERED AT 13:00:49 ON 11 JUL 2006
                D SAVED

     FILE 'BIOSIS' ENTERED AT 13:01:22 ON 11 JUL 2006
L141       73704 SEA ABB=ON  PLU=ON  (L70 OR L71 OR L72)(15A)(L132 OR L13)
L142        5560 SEA ABB=ON  PLU=ON  (L70 OR L71 OR L72)(15A)((L12 OR L14)(7A)L1
                25)
L143          46 SEA ABB=ON  PLU=ON  (L141 OR L142) AND L4
L144          18 SEA ABB=ON  PLU=ON  L143 AND L7
L145           2 SEA ABB=ON  PLU=ON  L144 AND (L10 OR L11 OR L41 OR L79 OR L80)
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                D SCAN

     FILE 'STNGUIDE' ENTERED AT 13:04:13 ON 11 JUL 2006

     FILE 'BIOSIS' ENTERED AT 13:05:04 ON 11 JUL 2006

     FILE 'REGISTRY' ENTERED AT 13:05:29 ON 11 JUL 2006
L146          23 SEA ABB=ON  PLU=ON  L4 NOT GENTAMICIN/CN

     FILE 'BIOSIS' ENTERED AT 13:05:48 ON 11 JUL 2006
L147          23 SEA ABB=ON  PLU=ON  (L141 OR L142) AND L146
L148           2 SEA ABB=ON  PLU=ON  L147 AND L7
                 SAVE TEMP L148 GIT372BIO1B/A
                 D SCAN

     FILE 'STNGUIDE' ENTERED AT 13:06:53 ON 11 JUL 2006

     FILE 'BIOSIS, PASCAL, JICST-EPLUS, CABA, LIFESCI, BIOENG, BIOTECHNO,
     BIOTECHDS, DRUGU, DRUGB, VETU, VETB, SCISEARCH, CONFSCI, DISSABS' ENTERED
     AT 13:07:28 ON 11 JUL 2006
L149       58726 SEA ABB=ON  PLU=ON  (L33 OR L34 OR L35 OR L46)(15A)(L10 OR L11
                 OR L41 OR L79 OR L80)
L150      199405 SEA ABB=ON  PLU=ON  (L70 OR L71) (10A)(L13 OR L132)
L151       14817 SEA ABB=ON  PLU=ON  (L70 OR L71) (10A)((L12 OR L14)(10A) L125)

L152         261 SEA ABB=ON  PLU=ON  L149 AND (L150 OR L151)

     FILE 'REGISTRY' ENTERED AT 13:22:55 ON 11 JUL 2006
                 SET SMARTSELECT ON
L153             SEL PLU=ON  L146 1- CHEM :      123 TERMS
                 SET SMARTSELECT OFF

     FILE 'BIOSIS, PASCAL, JICST-EPLUS, CABA, LIFESCI, BIOENG, BIOTECHNO,
     BIOTECHDS, DRUGU, DRUGB, VETU, VETB, SCISEARCH, CONFSCI, DISSABS' ENTERED
     AT 13:22:58 ON 11 JUL 2006
L154       49231 SEA ABB=ON  PLU=ON  L153
L155         137 SEA ABB=ON  PLU=ON  (L150 OR L151) AND L154
L156         103 SEA ABB=ON  PLU=ON  (L152 OR L155) AND L7
L157          35 SEA ABB=ON  PLU=ON  L156 AND (L41 OR L79 OR L80)
                 SAVE TEMP L157 GIT372MUL1B/A
L158         100 SEA ABB=ON  PLU=ON  L5 AND (L41 OR L79 OR L80)
L159          19 SEA ABB=ON  PLU=ON  L158 AND (LL12 OR L132 OR L14 OR L15)
L160          11 SEA ABB=ON  PLU=ON  L159 AND (L70 OR L71 OR L72)
                 SAVE TEMP L160 GIT372MULINV/A
                 D SAVED

     FILE 'STNGUIDE' ENTERED AT 13:43:53 ON 11 JUL 2006
                 D QUE STAT L78
                 D QUE STAT L97
                 D QUE STAT L119
                 D QUE STAT L140
                 D QUE STAT L148
                 D QUE STAT L157

     FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, JICST-EPLUS,
     LIFESCI, BIOENG, BIOTECHNO, BIOTECHDS, DRUGU, SCISEARCH' ENTERED AT
     13:45:32 ON 11 JUL 2006
L161         127 DUP REM L78 L97 L119 L140 L148 L157 (32 DUPLICATES REMOVED)
                   ANSWERS '1-26' FROM FILE HCAPLUS
                   ANSWERS '27-47' FROM FILE WPIX
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                    ANSWERS '48-75' FROM FILE MEDLINE
                    ANSWERS '76-113' FROM FILE EMBASE
                    ANSWER '114' FROM FILE PASCAL
                    ANSWERS '115-116' FROM FILE LIFESCI
                    ANSWER '117' FROM FILE BIOENG
                    ANSWERS '118-120' FROM FILE BIOTECHDS
                    ANSWERS '121-124' FROM FILE DRUGU
                    ANSWERS '125-127' FROM FILE SCISEARCH

     FILE 'STNGUIDE' ENTERED AT 13:45:50 ON 11 JUL 2006

     FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, PASCAL, LIFESCI, BIOENG, BIOTECHDS,
     DRUGU, SCISEARCH' ENTERED AT 13:46:19 ON 11 JUL 2006
               D IBIB ED AB HITIND HITSTR

     FILE 'STNGUIDE' ENTERED AT 13:46:22 ON 11 JUL 2006

     FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, PASCAL, LIFESCI, BIOENG, BIOTECHDS,
     DRUGU, SCISEARCH' ENTERED AT 13:46:42 ON 11 JUL 2006
               D IBIB ED AB HITIND HITSTR 2-26

     FILE 'STNGUIDE' ENTERED AT 13:46:50 ON 11 JUL 2006

     FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, PASCAL, LIFESCI, BIOENG, BIOTECHDS,
     DRUGU, SCISEARCH' ENTERED AT 13:47:59 ON 11 JUL 2006
               D IALL ABEQ TECH ABEX 27-47

     FILE 'STNGUIDE' ENTERED AT 13:48:46 ON 11 JUL 2006

     FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, PASCAL, LIFESCI, BIOENG, BIOTECHDS,
     DRUGU, SCISEARCH' ENTERED AT 13:49:55 ON 11 JUL 2006
               D IBIB ED AB HITIND 48-127

     FILE 'STNGUIDE' ENTERED AT 13:50:38 ON 11 JUL 2006
               D QUE L44
               D QUE L85
               D QUE L100
               D QUE L123
               D QUE L160

     FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH'
     ENTERED AT 13:52:31 ON 11 JUL 2006
L162          23 DUP REM L44 L85 L100 L123 L160 (22 DUPLICATES REMOVED)
                    ANSWERS '1-10' FROM FILE HCAPLUS
                    ANSWERS '11-12' FROM FILE WPIX
                    ANSWERS '13-17' FROM FILE MEDLINE
                    ANSWER '18' FROM FILE EMBASE
                    ANSWERS '19-23' FROM FILE BIOSIS

     FILE 'STNGUIDE' ENTERED AT 13:53:05 ON 11 JUL 2006

     FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:53:13 ON 11
     JUL 2006
               D IBIB ED AB 1-23

     FILE 'STNGUIDE' ENTERED AT 13:53:21 ON 11 JUL 2006

     FILE 'STNGUIDE' ENTERED AT 13:53:45 ON 11 JUL 2006
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FILE HOME

FILE ZCAPLUS

FILE COVERS 1907 - 11 Jul 2006 VOL 145 ISS 3
FILE LAST UPDATED: 10 Jul 2006 (20060710/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE HCAPLUS

FILE COVERS 1907 - 11 Jul 2006 VOL 145 ISS 3
FILE LAST UPDATED: 10 Jul 2006 (20060710/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE STNGUIDE
FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jul 7, 2006 (20060707/UP).

FILE WPIX
FILE LAST UPDATED: 6 JUL 2006 <20060706/UP>
MOST RECENT DERWENT UPDATE: 200643 <200643/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

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>>> PLEASE BE AWARE OF THE NEW IPC REFORM IN 2006, SEE
http://www.stn-international.de/stndatabases/details/ipc_reform.html and

http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf <<<

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http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<

FILE REGISTRY
Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 10 JUL 2006 HIGHEST RN 891779-14-9
DICTIONARY FILE UPDATES: 10 JUL 2006 HIGHEST RN 891779-14-9

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

FILE MEDLINE
FILE LAST UPDATED: 8 JUL 2006 (20060708/UP). FILE COVERS 1950 TO DATE.

On December 11, 2005, the 2006 MeSH terms were loaded.

The MEDLINE reload for 2006 is now (26 Feb.) available. For details on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

OLDMEDLINE is covered back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2006 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE EMBASE
FILE COVERS 1974 TO 11 Jul 2006 (20060711/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

EMBASE is now updated daily. SDI frequency remains weekly (default) and biweekly.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE BIOSIS
FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 5 July 2006 (20060705/ED)

FILE PASCAL
FILE LAST UPDATED: 10 JUL 2006 <20060710/UP>
FILE COVERS 1977 TO DATE.

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION IS AVAILABLE
IN THE BASIC INDEX (/BI) FIELD <<<

FILE JICST-EPLUS
FILE COVERS 1985 TO 10 JUL 2006 (20060710/ED)

THE JICST-EPLUS FILE HAS BEEN RELOADED TO REFLECT THE 1999 CONTROLLED
TERM (/CT) THESAURUS RELOAD.

FILE CABA
FILE COVERS 1973 TO 10 Jul 2006 (20060710/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

The CABA file was reloaded 7 December 2003. Enter HELP RLOAD for details.

FILE LIFESCI
FILE COVERS 1978 TO 21 Jun 2006 (20060621/ED)

FILE BIOENG
FILE LAST UPDATED: 21 JUN 2006 <20060621/UP>
FILE COVERS 1982 TO DATE

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION AVAILABLE IN
THE BASIC INDEX <<<

FILE BIOTECHNO
FILE LAST UPDATED: 7 JAN 2004 <20040107/UP>
FILE COVERS 1980 TO 2003.

>>> BIOTECHNO IS NO LONGER BEING UPDATED AS OF 2004 <<<

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION AVAILABLE IN
/CT AND BASIC INDEX <<<

FILE BIOTECHDS
FILE LAST UPDATED: 11 JUL 2006 <20060711/UP>
FILE COVERS 1982 TO DATE

>>> USE OF THIS FILE IS LIMITED TO BIOTECH SUBSCRIBERS <<<

FILE DRUGU
FILE LAST UPDATED: 10 JUL 2006 <20060710/UP>
>>> DERWENT DRUG FILE (SUBSCRIBER) <<<

>>> FILE COVERS 1983 TO DATE <<<
>>> THESAURUS AVAILABLE IN /CT <<<

FILE DRUGB
>>> FILE COVERS 1964 TO 1982 - CLOSED FILE <<<

FILE VETU
FILE LAST UPDATED: 02 JAN 2002 <20020102/UP>
FILE COVERS 1983-2001

FILE VETB
FILE LAST UPDATED: 25 SEP 94 <940925/UP>
FILE COVERS 1968-1982

FILE SCISEARCH

FILE COVERS 1974 TO 6 Jul 2006 (20060706/ED)

SCISEARCH has been reloaded, see HELP RLOAD for details.

FILE CONFSCI
FILE COVERS 1973 TO 10 Jul 2006 (20060710/ED)

CSA has resumed updates, see NEWS FILE

FILE DISSABS
FILE COVERS 1861 TO 21 JUN 2006 (20060621/ED)

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